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Treatment of Adrenal Insufficiency by Means of Subcutaneous Implants of Pellets of Desoxy-corticosterone Acetate (A Synthetic Adrenal Cortical Hormone), GEORGE W. THORN, LEWIS L. ENGEL AND HARRY EISENBERG 155

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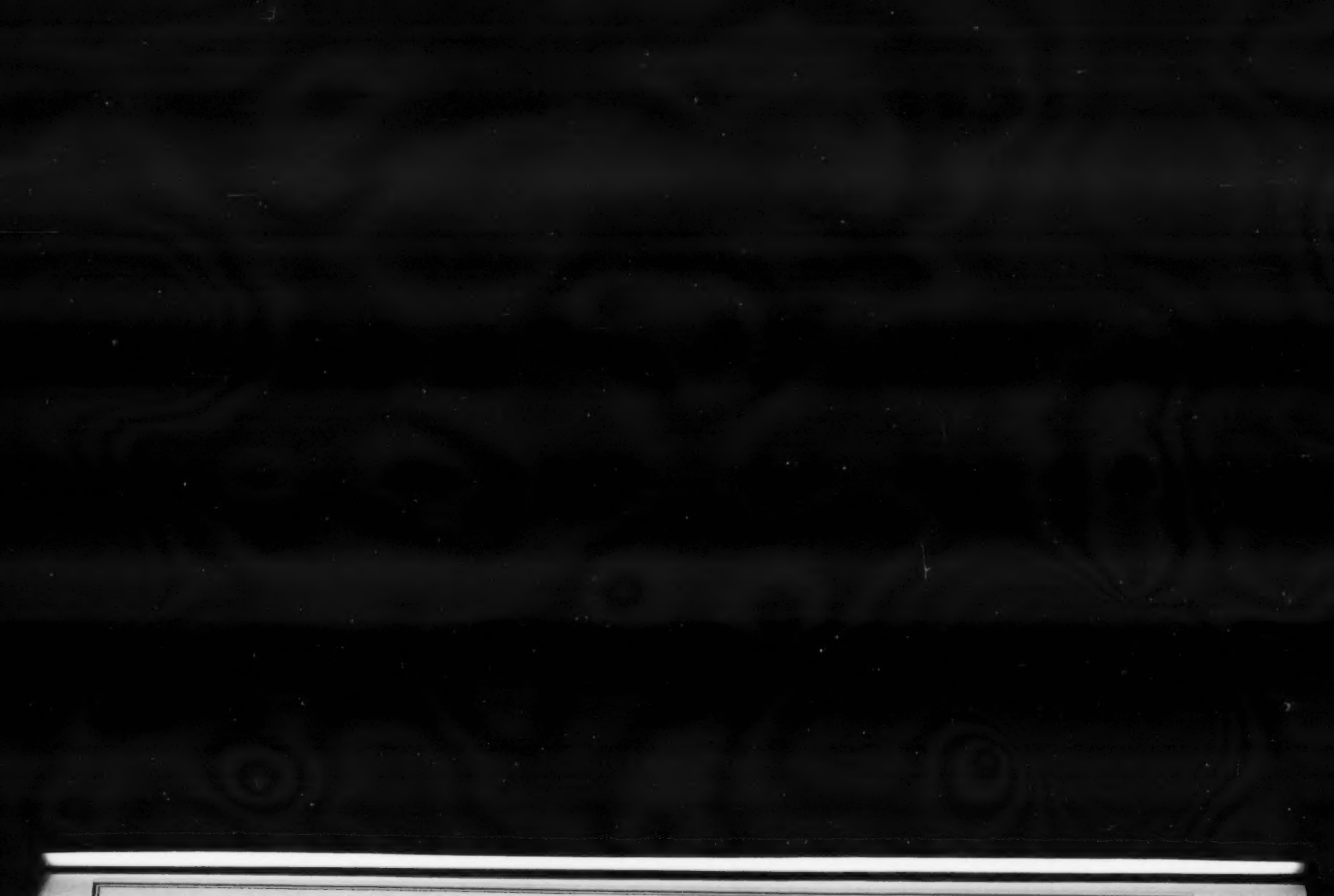

TREATMENT OF ADRENAL INSUFFICIENCY BY MEANS OF SUBCUTANEOUS IMPLANTS OF PELLETS OF DESOXY-CORTICOSTERONE ACETATE[1] (A SYNTHETIC[2] ADRENAL CORTICAL HORMONE)

GEORGE W. THORN, LEWIS L. ENGEL[3] AND HARRY EISENBERG

(From the Chemical Division, Medical Clinic, Johns Hopkins University and Hospital)

Submitted for publication February 6, 1939

It has been shown that bilaterally adrenalectomized dogs may be maintained in good health by means of daily subcutaneous injections of a solution of crystalline desoxy-corticosterone acetate in oil (2). Although injections of a solution of desoxy-corticosterone acetate in oil exert a prolonged effect (24 hours), it is by no means certain that a uniform liberation of hormone occurs throughout this period. To obviate the necessity of daily injections of hormone, to provide for more uniform and continued absorption, and if possible, to effect some economy in the requirement of hormone, pellets[4] composed of crystals of desoxy-corticosterone acetate have been implanted subcutaneously in adrenalectomized dogs maintained on a diet of low sodium and chloride content. Deanesly and Parkes (3) have reported that the subcutaneous implantation of tablets of estrogens and androgens produced a prolongation of the hormonal effect, and provided an efficient and convenient method of administration. Recently, Ingle and Mason (4) have succeeded in prolonging the survival period of adrenalectomized rats by implanting, subcutaneously, tablets composed of a mixture of cholesterol and compounds derived from the adrenal cortex.

[1] This study was aided by a grant from the Committee on Research in Endocrinology, National Research Council.

[2] Recently, Reichstein and von Euw (1) have succeeded in isolating desoxy-corticosterone from an extract of beef adrenals.

[3] John D. Archbold Fellow in Medicine.

[4] The authors are indebted to Doctor A. S. Parkes, The National Institute for Medical Research, London, for his valuable suggestions and assistance in the preparation of pellets.

EXPERIMENTAL METHODS

Normal dogs, approximately 10 kg. in weight, were kept in metabolism cages and provided with a constant diet of low sodium and chloride content. The care of the animals and the technic used in the metabolic studies have been described (2). After a control period of several days, during which the renal excretion and plasma concentration of electrolytes were measured, the animals were bilaterally adrenalectomized.[5] Following adrenalectomy the daily requirement of desoxy-corticosterone acetate[6] in oil was determined. After a positive sodium and chloride balance had been established, the daily injections of desoxy-corticosterone acetate in oil were discontinued and, under local anesthesia, one or more pellets of the hormone were inserted subcutaneously through a small incision in the skin (Fig. 1). The number and size of pellets necessary to maintain the animal were determined by trial. A loss in body weight and an increase in the renal excretion of sodium and chloride (24 hours) provided the first evidence of insufficient treatment. After a period during which the animals were maintained in excellent condition, the pellets were removed under local anesthesia, dried and weighed. Following the removal of the pellets the animals rapidly (48–72 hours) developed signs and symptoms of adrenal insufficiency. At this time the pellets were implanted again and the animals recovered promptly.

Under sterile conditions the pellets were prepared by pounding a suitable quantity of crystalline desoxy-corticosterone acetate in a specially constructed mold (Fig. 1). Since no substance other than crystalline hormone was employed in the preparation of the pellets the weight loss of the pellets provided an accurate index of the amount of hormone liberated during any given period. The hardness of the pellets permitted several implantations and withdrawals without disintegration. Pellets have remained intact in animals for more

[5] Under spinal anesthesia a single stage bilateral adrenalectomy was performed by Doctor Warfield M. Firor of the Department of Surgery. We wish to acknowledge our appreciation of his assistance and coöperation in this study.

[6] The synthetic crystalline desoxy-corticosterone acetate used in this study was supplied by Messrs. Ciba through the courtesy of Doctors K. Miescher and E. Oppenheimer.

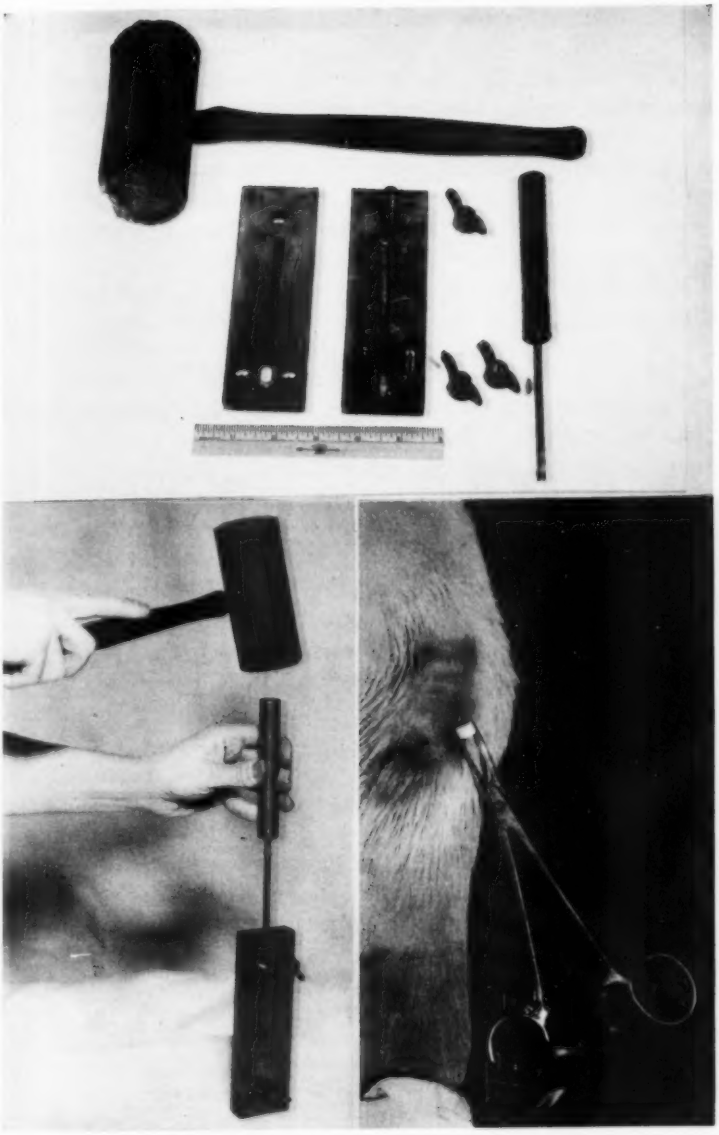

FIG. 1. THE PREPARATION AND INSERTION OF A PELLET OF DESOXY-CORTICOSTERONE ACETATE

than four months. Pellets weighing 60–200 mg., and measuring 6.5 mm. in diameter by 2.0–6.0 mm. in thickness were found to be of convenient size. The surface area of pellets of this size varied from 107.2 sq. mm. (2.0 mm. in thickness) to 188.9 sq. mm. (6.0 mm. in thickness). Although the "life" of a pellet depends upon its consistency and its weight, the quantity of hormone liberated appears to vary with the surface area of the pellet.

No untoward local reaction was observed at the site of implantation. The location of the pellets may be marked by silver wire.

OBSERVATIONS

The daily subcutaneous injection of 1.5 mg. of a solution of desoxycorticosterone acetate in sesame oil was sufficient to maintain the body weight, electrolyte balance and normal plasma concentration of electrolytes in Dog 211 (Chart 1).[7] After nine days, injections of hormone were discontinued and one pellet of crystalline desoxycorticosterone acetate, weighing 82.5 mg. was implanted. This pellet was not sufficient for maintenance, for the animal lost weight, and a slight increase in the renal excretion of sodium and chloride was observed. Five days after the first pellet was implanted, a second pellet, weighing 110.5 mg. was inserted, the first pellet being left *in situ*. A marked retention of sodium and chloride and a rapid increase in the animal's weight followed the implantation of the second pellet. Eighteen days after the implantation of the second pellet the animal's condition was excellent, his appetite was good, his weight was significantly above that of the control period and the blood level of electrolytes was normal. At this time both pellets were removed, dried and weighed. The first pellet which at the beginning of the experiment had weighed 82.5 mg. was found to weigh 75.9 mg., a loss of 6.6 mg., amounting to an average daily loss of 0.3 mg. The weight of the second pellet decreased from 110.5 mg. to 101.5 mg., a loss of 9.0 mg. in 18 days, or 0.5 mg. daily. Thus during a period

[7] Throughout the studies demonstrated in Charts 1, 2 and 3, the animals were maintained on a diet of low sodium and chloride content. By analysis the diet was found to contain 14.1 m.eq. of sodium, 12.3 m.eq. of chloride, 19.8 m.eq. of potassium, 0.550 gm. of total phosphorus and 11.48 gm. of total nitrogen per day.

of eighteen days approximately 0.8–0.9 mg. of hormone daily had been supplied by the two pellets. Previous experiments had indicated that the hormonal requirement of this animal was 1.5 mg. daily

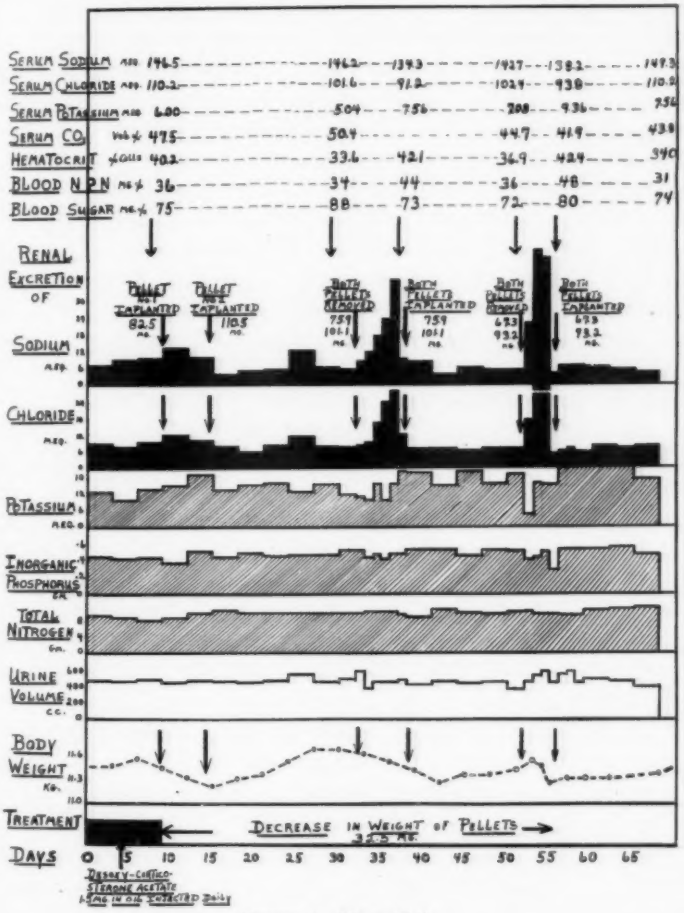

CHART 1. (DOG 211)

by subcutaneous injection in oil. Thus the animal was maintained in excellent condition without the necessity of daily injections and in addition a considerable saving in hormone was accomplished.

Subsequently the removal of both pellets was followed by weight loss and a marked increase in the renal excretion of sodium and chloride. The serum concentration of sodium decreased from 146.2 to 134.3 and the serum chloride from 101.6 to 91.2 m.eq. per titer. Potassium was retained and the plasma concentration of potassium increased from 5.04 to 7.56 m.eq. per liter. Marked hemoconcentration occurred, the volume of packed cells increasing from 33.6 per cent to 42.1 per cent. At this time the animal appeared weak and his appetite was poor. Five days after removal, the pellets were reimplanted. Following this a striking retention of sodium and chloride was noted and the condition of the animal improved. It was thought that the return to normal would be a slow process since the daily quantity of hormone available from the pellets only slightly exceeded the maintenance dose. It is likely that the increased supply of hormone made available by small particles of pellet unavoidably broken off during the process of implantation accounted for the rapid improvement. Upon dissecting a pellet from the surrounding tissue for the purpose of removing it, enough particles may be broken off to provide a supply of hormone for 2–3 days, thus delaying the onset of signs and symptoms of adrenal insufficiency. It is obvious that manipulation of the pellets materially increases the apparent rate of utilization, and that the withdrawal periods increase temporarily the animal's requirement of hormone.

It requires a considerable period of time for an animal maintained on a restricted intake of sodium and chloride to replace the tremendous depletion of these ions which withdrawal of treatment occasions. However, fifteen days after the second implantation of the pellets, as the result of a markedly positive sodium and chloride balance, it was noted that the animal's weight had returned to normal and the plasma concentration of electrolytes approximated that observed during the control period (Chart 1).

At this time a second removal of the pellets was accomplished successfully and was followed by the same changes as those noted after the first withdrawal. This time the pellets were found to weigh 67.3 and 93.2 mg. respectively. This represented a loss of 8.6 and 7.9 mg. respectively or a total of 16.5 mg. during the fifteen day period (1.1 mg., average daily loss). The decrease in the weight of the

pellets approximated closely that noted during the first period (0.8–0.9 mg. average daily loss) and again represented a considerable saving over the quantity of hormone required by daily injection (1.5 mg.).

Following a third implantation of the pellets, the animal was maintained in excellent condition for a period of 16 days. At this time a third pellet (54.3 mg.) was inserted. Forty-seven days later, the third pellet was found to weigh 38.5 mg., a loss of 15.8 mg. If one assumes that the two remaining pellets lost proportionally, a total of approximately 50 mg. of desoxy-corticosterone acetate were provided by the pellets during a 47 day period. This amounts to approximately 1 mg. daily.

This animal is now in excellent condition four months after the original pellets were inserted. At no time during this study was sodium or chloride added to the diet. The animal now weighs 12.65 kg. in comparison to 11.45 kg. at the beginning of the experiment. The plasma concentration of electrolytes is normal and the animal is in a positive sodium and chloride balance. The episodes of adrenal insufficiency which followed removal of the pellets indicate the completeness of adrenalectomy.

In a second experiment of this type (Dog 210, Chart 2) it was noted that the daily injection of 1 mg. of desoxy-corticosterone acetate in oil was just sufficient to maintain the body weight of the animal. The daily injection of 1.5 mg. of hormone was associated with a marked retention of sodium and chloride and an increase in body weight. On the seventh day of the experiment, the daily injections of hormone were discontinued and two pellets (66.1 and 76.0 mg.) were implanted subcutaneously. Following this the animal continued to gain weight and to retain sodium and chloride. Ten days after the insertion of the pellets a considerable rise in the serum concentration of sodium had occurred (Chart 2). Removal of both pellets at this time resulted in a marked increase in the renal excretion of sodium and chloride, a decrease in the excretion of potassium, and loss in weight. Serum sodium decreased from a concentration of 152.3 to 124.7, serum chloride from 107.2 to 100.6 and serum potassium increased from 6.00 to 7.32 m.eq. per liter and marked hemoconcentration occurred.

The weights of the pellets at this time were 59.6 and 72.7 mg., a decrease of 6.5 and 3.3 mg. respectively. Thus a total decrease of

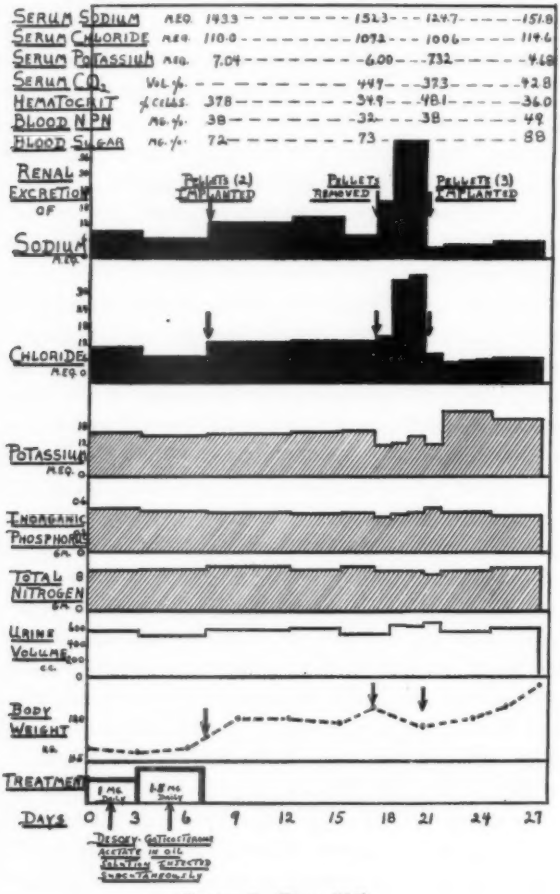
SERUM SODIUM MEQ. 1433 — 1523 — 1247 — 1518
SERUM CHLORIDE MEQ. 110.0 — 1072 — 1006 — 1196
SERUM POTASSIUM MEQ. 7.04 — 6.00 — 7.32 — 9.68
SERUM CO2 VOL. % 44.9 — 37.3 — 92.8
HEMATOCRIT % CELLS. 37.8 — 34.9 — 48.1 — 36.0
BLOOD NPN MG. % 38 — 32 — 38 — 49
BLOOD SUGAR MG. % 72 — 73 — 88
RENAL EXCRETION OF
PELLETS (2) IMPLANTED
PELLETS REMOVED
PELLETS (3) IMPLANTED
SODIUM MEQ.
CHLORIDE MEQ.
POTASSIUM MEQ.
INORGANIC PHOSPHORUS GM.
TOTAL NITROGEN GM.
URINE VOLUME CC.
BODY WEIGHT KG.
TREATMENT
1 MG. DAILY
1.8 MG. DAILY
DAYS 0 3 6 9 12 15 18 21 24 27
DESOXY-CORTICOSTERONE ACETATE IN OIL SOLUTION INJECTED SUBCUTANEOUSLY

CHART 2. (DOG 210)

9.8 mg. had occurred during a ten day period (an average daily loss of approximately 1 mg.).

After a three-day withdrawal period, *three pellets* were inserted, the weights being 59.6, 72.7 and 59.3 mg. The implantation of three

pellets resulted in a very marked sodium and chloride retention, increased potassium excretion, a rapid gain in weight and a restoration of the plasma concentration of electrolytes to normal. Marked plasma dilution occurred. On this regimen the animal has been kept in excellent condition for more than three months. It is probable that the three pellets provide a quantity of hormone considerably greater than that needed for maintenance since the animal has continued to gain weight rather rapidly and at present weighs 15.0 kg. (a total gain of 3.3 kg.).

Two of the pellets removed 60 days after implantation weighed 49.8 mg. (previously 72.7 mg.) and 38.5 mg. (previously 59.6 mg.), the total loss of the two pellets amounting to 44.0 mg. If it can be assumed that the third pellet (59.3 mg.) lost weight at the same rate, then the total hormone provided by the three pellets during the 60 days approximated 66 mg. or 1.1 mg. per day. Previous experience had demonstrated that a daily injection of 1.5 mg. of desoxy-corticosterone acetate in oil was necessary to produce a similar effect in this animal. In this experiment a saving of 25–30 per cent was accomplished and the necessity for daily injections was obviated. Throughout this experiment the diet was low in sodium and chloride.

In a third experiment (Dog 215, Chart 3) similar results were obtained. The daily requirement of hormone in oil, injected subcutaneously, was 1.5 mg. Daily injections were discontinued and two pellets (173.0 and 67.0 mg.) were inserted. The animal gained weight, retained sodium and chloride and maintained a normal concentration of plasma electrolytes. Eight days after insertion, both pellets were removed and found to weight 170.5 and 56.0 mg. respectively. A total loss of 13.5 mg. had occurred during the eight days (1.7 mg. per day). It should be noted that fragmentation of the smaller pellet had apparently occurred during implantation. This probably accounted for the greater loss in weight of this pellet. As in the previous experiments, removal of the pellets was followed by an increased sodium and chloride excretion, loss of weight and the appearance of signs of adrenal insufficiency, but in this instance, the changes occurred more gradually than when the entire source of hormone was removed. Seven days after the removal of both pellets, a single pellet (170.5 mg.) was reinserted. Subsequently, the animal

gained weight, a positive sodium and chloride balance was noted and the concentration of sodium and chloride in the plasma returned to normal. Thirty-two days after the latter pellet had been inserted it was removed and found to weigh 158.5 mg., a loss of 12 mg. A total of 25.5 mg. (13.5 and 12.0 mg.) was supplied by pellets during a 40 day period, or 0.7 mg. per day. This represented a considerable saving of hormone. The animal has now been maintained in excellent condition for three months by means of pellets. Throughout this study the animal was fed a diet low in sodium and chloride. At pres-

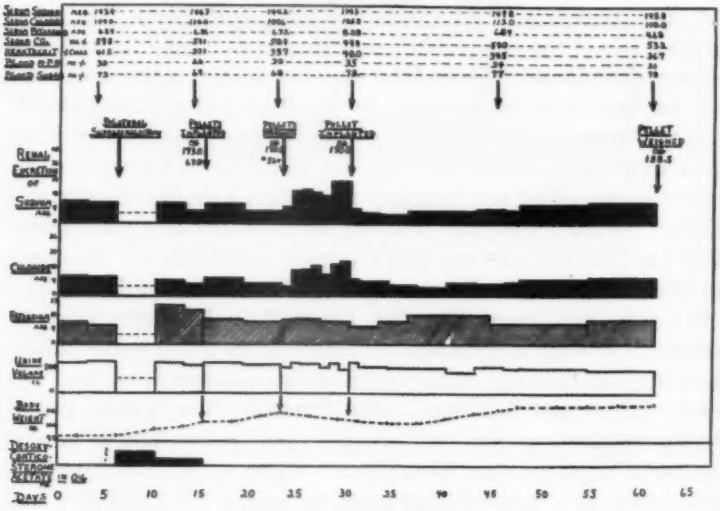

CHART 3. (DOG 215)

ent the plasma concentration of electrolytes is normal and the animal weighs 11.60 kg. in comparison to 10.20 kg. at the beginning of the experiment.

In a fourth experiment, Dog 217, 9.75 kg. in weight, required 1.3–1.5 mg. per day of desoxy-corticosterone acetate injected in oil. Injections of hormone were discontinued and two pellets (84.6 and 69.6 mg.) were implanted. Fourteen days later the animal was found to have a normal serum concentration of electrolytes. During this period he had gained 0.55 kg. and had maintained a positive sodium

and chloride balance. At this time both pellets were removed and were found to weigh 77.5 and 63.5 mg., a loss of 7.1 and 6.1 mg. respectively. A total loss of 13.2 mg. had occurred during the 14 day period (0.9 mg. per day). A considerable saving in hormone had resulted from the implantation of pellets since this dog required 1.3–1.5 mg. per day of hormone in oil injected subcutaneously. Removal of the pellets was associated with increased sodium and chloride excretion, potassium retention and hemoconcentration. At present the animal is being maintained in good condition following reimplantation of the same pellets.

DISCUSSION

The implantation of pellets of desoxy-corticosterone acetate appears to be an advantageous method of administering hormone to adrenalectomized dogs. Since the pellets are composed solely of desoxy-corticosterone acetate an accurate measurement of the hormone supplied may be obtained by weighing the pellets after they are removed from the animal. It is obvious that a single large pellet presenting a surface area equal to that of several smaller pellets would provide a continuous supply of hormone over a longer period. The limited supply of crystalline material at hand during these studies necessitated the utilization of smaller pellets since a greater surface area would thus be provided by the same quantity of material.

To ensure successful treatment it is necessary only to be certain that the minimum requirement is exceeded since a moderate excess of hormone apparently occasions no untoward effect.

The favorable results obtained in adrenalectomized dogs following implantation of pellets of desoxy-corticosterone acetate suggest the possibility of employing this technic in the treatment of patients with Addison's disease. Studies on four patients with Addison's disease indicate that the effect of the pellets appears to be as striking in patients as in adrenalectomized dogs. These studies will be reported in detail at a later date.

SUMMARY

Bilaterally adrenalectomized dogs, fed a constant diet of low sodium and chloride content, may be maintained in excellent condition, by

means of the subcutaneous implantation of pellets of crystalline desoxy-corticosterone acetate. Removal of the pellets is followed by increased renal excretion of sodium and chloride, weight loss, hemoconcentration, potassium retention and a decrease in the plasma concentration of sodium and chloride. Implantation of the pellets results in a prompt and striking decrease in the renal excretion of sodium and chloride, increased potassium excretion, restoration of plasma electrolytes to normal, improved appetite, and weight gain. The quantity of hormone provided by pellets may be determined by removing the pellets and weighing them. Experiments indicate that a considerable saving in hormone may be effected by the use of this method of administration.

We wish to acknowledge the technical assistance of Kay Eisenberg and William Sause in these studies.

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GRADED PNEUMONECTOMY IN THE TREATMENT OF TUMORS OF THE LUNG

WILLIAM FRANCIS RIENHOFF, JR.

(From the Department of Surgery of the Johns Hopkins University Medical School)

Submitted for publication January 15, 1939

The successful treatment of malignant tumors of the lung, and of those benign tumors which involve the primary bronchus rather extensively, can be accomplished only by complete removal of the lung together with its lymphatic vessels and glands. In the treatment of malignant tumors, lobectomy has been uniformly unsatisfactory owing to local recurrences. Any plan of operation should take into consideration the fact that in the majority of cases it will be necessary to amputate the primary bronchus close to the trachea in order to circumvent the tumor. This can be accomplished only by total pneumonectomy.

The operation which is about to be described has been designated *graded pneumonectomy*. The procedure has been divided into several steps or grades, thus permitting the interruption of the operation at one or several points when the condition of the patient does not warrant a complete one stage procedure. It is important to emphasize our belief that the operation should be completed in one stage if the condition of the patient permits. Unfortunately the current methods of preoperative examination are not adequate for selection of such patients in advance. The extensiveness of the intrathoracic disease, the degree of diminution of the patient's physiological reserve, the liability of development of inexplicable states of shock are important but unpredictable factors. A plan of operation flexible enough to cope with complications arising during the operation is obviously desirable. A graded pneumonectomy has flexibility in that it may be interrupted at designated points, without loss of ground and without the development of gangrene of the lung or empyema during the period of interruption.

The purpose of this paper is two-fold: first, to describe the operative procedure now employed in total pneumonectomy, indicating the points at which the operation may be interrupted with safety to the patient; secondly, to emphasize the importance of a method of closure of the primary bronchus which has been found by trial and error to be successful. While the importance of each of the successive steps in the operative technique of total pneumonectomy is recognised, nevertheless, as Heuer (1) has stated, "One of the most important problems in lobectomy and pneumonectomy—the aseptic division and secure closure of the bronchial stump—has been neglected during the period of the development of the multiple stage operation and in my opinion still is not satisfactorily solved. It again comes clearly into the foreground and to its solution we should continue to apply ourselves." This detail in the operative technique is the *sine qua non* of a successful pneumonectomy.

RESULTS OF OPERATION

In twenty patients total pneumonectomy has been carried out successfully by the operative technique herein described. In this series of patients there have been two deaths. One occurred 14 days after the second stage of the operation and was thought to be due to a failure of the peripheral circulatory system, closely resembling delayed shock. The second death followed a one-stage total pneumonectomy, one week after operation. The patient died of coronary thrombosis, proved at autopsy. Although the operative field had healed *per primum* throughout, examination of the heart revealed the evidence of long standing coronary disease. It was felt that although this case must be included in computing the mortality rate, nevertheless, the operation had had very little to do with the death of the patient. In both of the foregoing instances the bronchus had healed completely and there was no infection of the pleural cavity. Because of these two deaths the mortality rate must be considered as 10 per cent. In the series of 20 cases only the last 7 have been consecutive hospital admissions. The previous 13 were operated upon during a period of five years. The method of closure of the bronchus employed routinely at the present time and in the last 7 cases was used also in the previous 13 patients. In other cases,

during this same period, the bronchial stump was occluded in different ways, using various types of suture material, with the result that leakage from the bronchus occurred in some instances, leading to a higher percentage of postoperative complications and a higher mortality rate. In the 20 cases under consideration, there have been no instances of leakage of the bronchial stump and in all, the incisions have healed throughout *per primum*. Eight of these patients were operated upon in two stages.

PREOPERATIVE PREPARATION

The proper preoperative preparation of the patient, described previously (2, 3, 4), results not only in protection from bacterial invasion, and in acceleration of postoperative healing, but also brings about a reduction in the mass of lung tissue to be handled, thus facilitating the operation. The introduction of air into the pleural cavity in order to bring about a preoperative collapse of the lung, is attempted in all cases and is accomplished in the great majority. As pointed out in the previous reports, the value of this procedure cannot be overestimated. The presence or absence of intrapleural adhesions, as well as fixation of the mediastinum may be demonstrated in this manner and pertinent modifications in the operative procedure thus anticipated. The technical advantages of removing a collapsed lung, rather than an inflated one, are obvious. The physiological benefits derived from preoperative disuse of one lung and from the adaptation of the circulatory mechanism to an increased intrathoracic pressure, are so fully appreciated as to make further discussion superfluous.

Injection into the pleural cavity of 50 cc. of beef infusion broth, pH 7.45, containing 1 per cent peptone, has been used routinely in all cases in which it has been possible to bring about a preoperative collapse of the lung. This injection is made 48 to 72 hours before operation and serves a two-fold purpose, protecting the patient against infection, and acting as a stimulus to the formation of granulation tissue, the exudation of plasma, and the obliteration of the dead space which will result from the removal of the lung. Following the injection of broth there is not only a local, but a constitutional reaction. The temperature, as a rule, rises 1° to 2°F. and this is accompanied by an increase in the leucocyte count of the blood to about 15,000.

After 48 hours the fever subsides, but the increase in the leucocyte count persists. At the same time there is a slight effusion of fluid into the thoracic cavity which contains the broth. This is one manifestation of a fibrinous pleurisy. Repeated daily thoracenteses with withdrawal of small amounts of this fluid for the purpose of making cell counts, has revealed a very high proportion of young polymorphonuclear leucocytes which reaches its maximum in from 48 to 72 hours. The average count is 25,000 cells per cubic mm., of which 85 per cent are polymorphonuclear and 15 per cent mononuclear. The ratio changes after 72 hours in favor of the mononuclear, both large and small. At the end of one week the latter not infrequently predominate. Associated with this cell-laden effusion the thoracic cavity is almost immediately lined with fibrin which completely covers the exposed pleural surfaces. After 24 hours many endothelial sprouts may be seen pushing their way into this scaffolding of fibrinous exudate, and after 48 hours the sprouts have developed lumina which are filled with red blood cells. In other words, a lining layer of granulation tissue has been formed. In this manner a preoperative mobilization of the combative and defensive inflammatory processes of the body against local thoracic and general blood stream invasion has been accomplished. Following operations such as total pneumonectomy for carcinoma of the lung or partial pneumonectomy for suppurative lesions of one lobe, there has never been, in our patients, a case of generalized empyema or mediastinitis. There has always been a postoperative accumulation of sero-sanguineous fluid of varying amounts which partially fills the dead space left immediately following operation. This serous fluid has a pronounced bacteriostatic effect particularly upon members of the pneumococcus and streptococcus groups. As a result of the operative trauma, the original plasma which has exuded in response to stimulation by the injected broth, is added to by a serous exudate containing erythrocytes. This accumulation of fluid seems to have a sterilizing or at least an inhibiting effect upon bacterial growth. Obliteration of the dead space following operation is more rapid in the absence of pus formation: the fibrin is preserved and forms a scaffold for the ingrowth of fibroblasts and endothelium. This finally results in the formation of a multilocular cystic, fibrous body which occupies the previously empty thoracic space. The bacteriostatic effect of the sero-sanguineous fluid prevents

the accumulation of those bacteriolytic and cytolytic products which inhibit new tissue formation, and thus the reparative and constructive processes are accelerated.

ANESTHESIA

After employing various mixtures of basal, general and local anaesthetics the combination of nembutal and cyclopropane has been found to be the most satisfactory. 0.2 Gm. of nembutal is administered by mouth the night before operation, to be followed by 0.3 Gm. *per rectum* the following morning. This amount of the drug causes sufficient narcosis for the patient to be transported to the operating suite in a semistuporous state, thus avoiding the effects of apprehension. Surgical anaesthesia is then induced by means of cyclopropane delivered from a closed gas circuit, through a tight-fitting mask. It was formerly our custom, in the majority of cases, to employ an intratracheal catheter, but since the routine adoption of an initial encircling ligature about the primary bronchus near the bifurcation of the trachea, we have considered the intratracheal tube to be unnecessary. The possibility of introducing infective agents into the trachea along with the tube can not be denied, and a further deleterious and even dangerous effect is the trauma to the mucous membrane of the pharynx and larynx which occurs no matter how carefully and gently the tube may be introduced. There have been no instances of postoperative pneumonia since the newer method of anaesthesization has been employed. It should be noted that ligation of the bronchus early in the operation prevents the manual expression of material from the affected into the unaffected lung. This tends to minimize the necessity for intratracheal aspiration by the anaesthetist during the operation. When the closed system with the tight-fitting mask is used, positive intratracheal and intrapulmonic pressure may be created as readily as with the intratracheal catheter.

OPERATIVE TECHNIQUE AND POSTOPERATIVE TREATMENT

The successive steps in the operation will be described as they are carried out in a one-stage pneumonectomy. The points will be indicated at which the operation may be interrupted in order to perform a graded pneumonectomy.

As previously reported access to the hilus of the lung by the anterior

route has been found to have many advantages over the lateral or posterior approaches. The incision is made over the third intercostal space, anteriorly, extending from the lateral border of the sternum to the anterior axillary line (Fig. 1). After dividing the pectoral muscles the internal intercostal muscles are incised about midway between the 3rd and 4th ribs, thus avoiding the intercostal vessels and nerves (Fig. 2). The pleural cavity is quickly opened by cutting through the parietal pleura for the entire length of the incision and the opening into the chest is further widened by means of a self-retained retractor or rib spreader (Fig. 3). Thus, complete exposure of the hilus of the lung is obtained with minimum operative trauma or loss of time. Resection of the ribs is entirely unnecessary because anteriorly the ribs are farther apart than elsewhere in the thoracic cage, and furthermore if the proper type of rib-spreader is used, they may be disarticulated at the costochondral junctions by gently spreading the retractor blades farther apart. Disarticulation of the costochondral junction of the 3rd and 4th ribs is accomplished with ease and rapidity. If further exposure is desirable the incision may be lengthened laterally to the midaxillary line and with a retractor possessing a deeper blade the 2nd and 5th ribs, as well as the 3rd and 4th, may be readily disarticulated. When the ribs are reapproximated during closure they are realigned with the costal cartilages and held in position by means of pericostal sutures (Fig. 15).

The advantages of the anterior approach cannot be overestimated. The invasion, or lack of invasion of the hilus of the lung and mediastinum may be ascertained at once, even when the remainder of the pleural cavity is practically sealed off by adhesions. The rapidity of the opening of the thoracic cavity is much greater than when other methods of approach are used. A truly high ligation of the pulmonary artery in the mediastinum, performed with great facility and celerity through the anterior incision, can be accomplished only with difficulty by a posterior approach because the pulmonary artery arises anterior to the primary bronchus (Fig. 4). On this point hangs the ability to ligate the bronchus high up near the bifurcation of the trachea, insuring the safety and efficacy of a pneumonectomy especially when the growth approximates the carina.

In the beginning of the operation the mediastinal pleura is incised

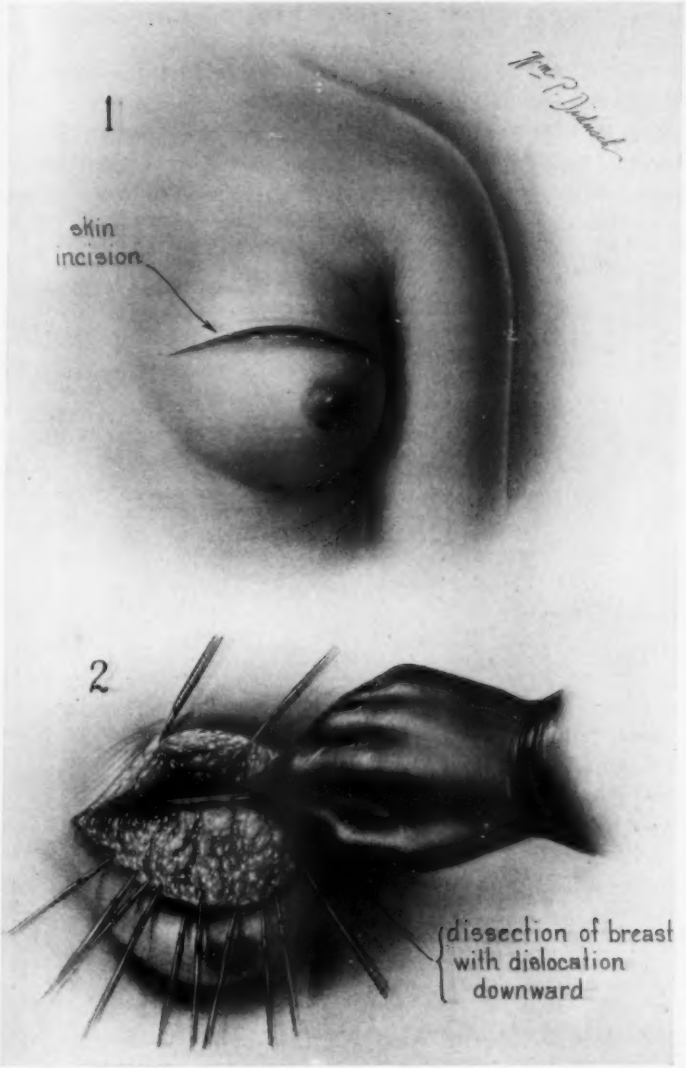

FIG. 1. LOCATION OF SKIN INCISION

The incision is in the region normally covered by the brassiere in the female. It is, of course, possible to make this incision below the nipple line and dislocate the breast upward instead of downward.

and dissected medialward together with the underlying areolar tissue, thus exposing the pulmonary artery (Fig. 5). The point at which the mediastinal pleura is incised varies, depending upon whether the operation is performed on the right or the left side. On the right the guiding landmark is the azygos vein, since the right pulmonary artery

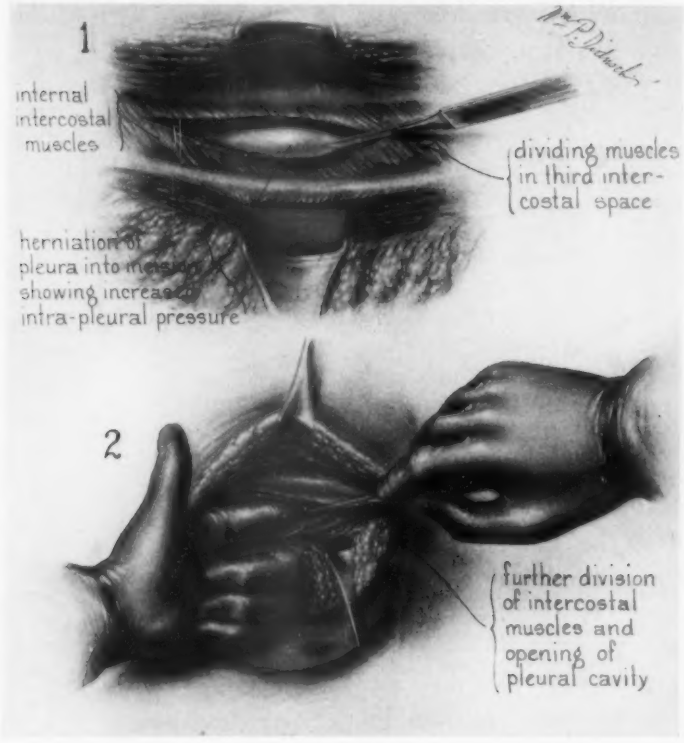
1
internal intercostal muscles
dividing muscles in third intercostal space
herniation of pleura into mediastinum showing increased intra-pleural pressure
2
further division of intercostal muscles and opening of pleural cavity

FIG. 2

emerges into the pleural cavity just inferior to this structure (Figs. 5 and 6). On the left side the pulmonary artery runs beneath the arch of the aorta (Figs. 6 and 7). The upper or superior surface of the pulmonary artery is immediately exposed and by means of careful blunt dissection, mainly with the index finger, the superior and pos-

terior surfaces are freed from the underlying bronchus (Fig. 8). The inferior surface is then dissected away from the upper border of the superior pulmonary vein and a no. 10 oiled braided-silk ligature is passed around the mediastinal portion of the vessel at least 2 to 3 cm. proximal to its intrathoracic branches (Fig. 9). After the first ligature is pulled home another is placed about the vessel 0.5 cm. distal

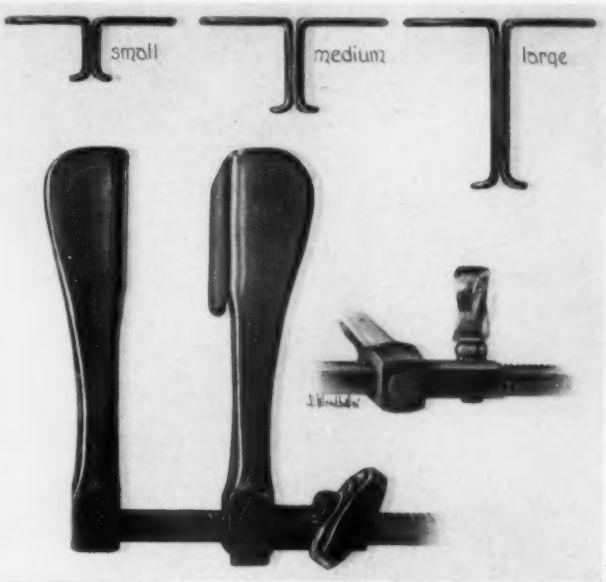

FIG. 3. Self-retaining retractors with different sized blades and the set screw to hold the retractor at any particular point of spread of the blades. It is impossible to obtain the proper exposure unless a self-retaining retractor is employed. (*Reduced to one-half actual size.*)

to the primary ligature, and this is likewise tied in a square knot. The loose ends of these ligatures are cut at least 6 cm. long so that they and the obliterated pulmonary artery may be easily recognized if a second stage operation is found to be necessary. The phrenic nerve is crushed in order to allow a temporary elevation of the diaphragm with consequent partial obliteration of the thoracic cavity on the

affected side. The absence of the piston action of the diaphragm resulting from this temporary paralysis aids in maintaining a more perfect collapse of the lung between the first and second stage. It also diminishes the possibility of dissemination of malignant emboli

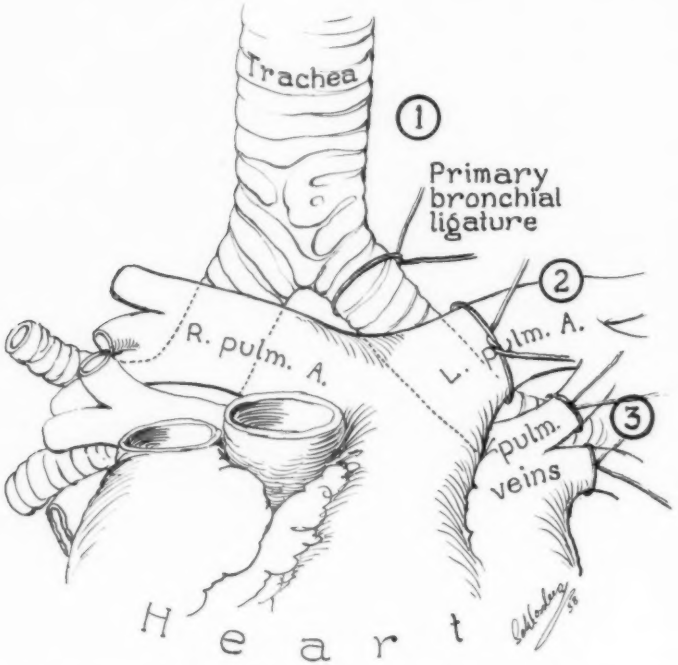

FIG. 4. RELATION OF PRIMARY BRONCHI TO PULMONARY ARTERIES AND VEINS

Various points at which ligatures are placed are designated by nos. 1, 2 & 3. No. 1 shows the site of the primary encircling ligature of the main bronchus, or step 2 in the operation. The first step is placing the ligature about the artery at point no. 2, in the diagram. The 3rd step in the operation consists in ligating the pulmonary veins.

by the expanding lung. The primary bronchus is then stripped of all the bronchial lymphatic glands and peribronchial connective tissue, from the bifurcation of the trachea to the point at which the pulmonary artery crosses the bronchus and takes up a position posterior

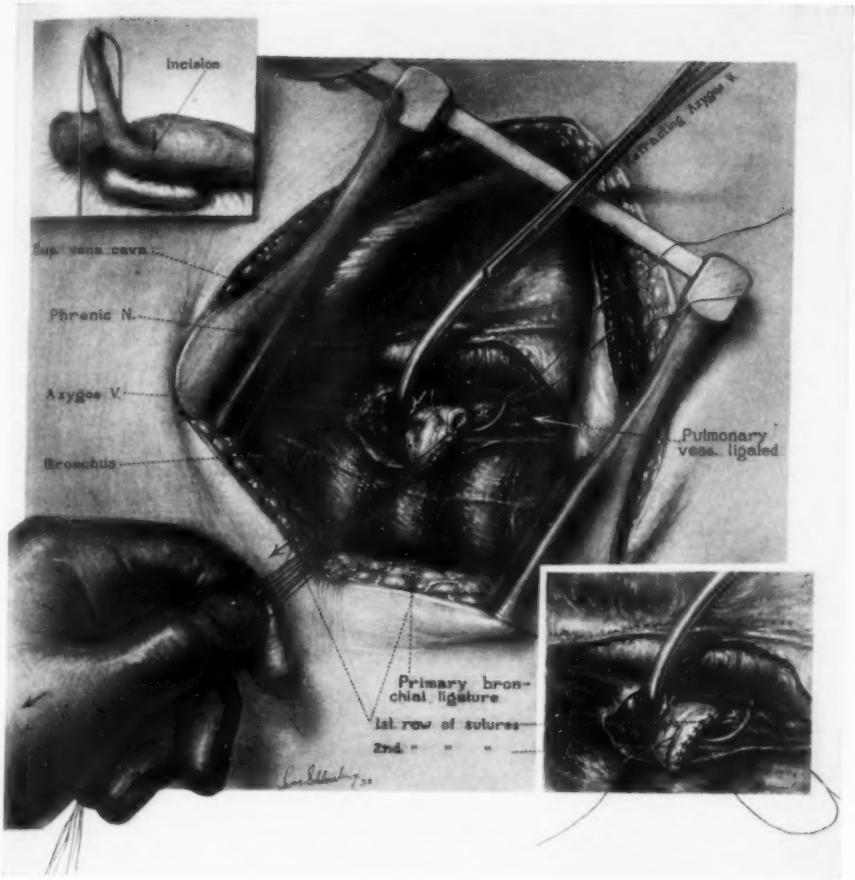

FIG. 5. In the *upper left corner* the position of the patient on the operating table is demonstrated. The side to be operated upon should be slightly more elevated than shown in the drawing, approximately 45° elevation. In the *middle drawing* the self-retaining retractor is shown in place. The curved clamp demonstrates the method by which the assistant holds the azygos vein and the superior vena cava away from the site of the primary encircling ligature about the primary bronchus just distal to the bifurcation of the trachea. The first incompleted row of interrupted silk sutures closing the end of the bronchial stump is shown. Immediately above the curve of the needle may be seen the ligated end of the right pulmonary artery and below it the ligated ends of the superior and inferior pulmonary veins. In the *lower right corner* the second incompleted row of mattress sutures is shown. When the posterior membranous portion of the bronchus is sutured to the anterior cartilaginous wall there is a tendency towards flattening of the stump. This brings about a more perfect approximation of the mucous membrane of the bronchus, with a minimum amount of tension on the suture line. The primary encircling ligature may be seen again, as in the middle drawing, higher up on the main bronchus.

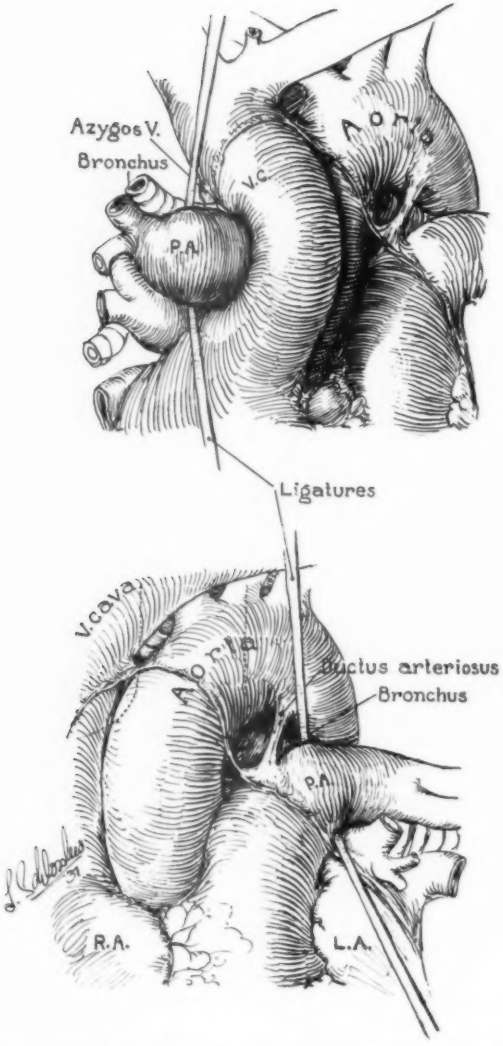

FIG. 6. DIAGRAMMATIC SKETCH SHOWING LOCATION OF THE LIGATURES FOR RIGHT AND LEFT PULMONARY ARTERIES

These are placed around each artery in the mediastinum, proximal to the intrathoracic branches.

to this structure. The bronchial glands are more easily detected than lymphatic glands elsewhere in the body, and because of their black pigmentation, metastases to them, as a rule, appear as white spots on their surface. A ligature of no. 10 braided silk is placed

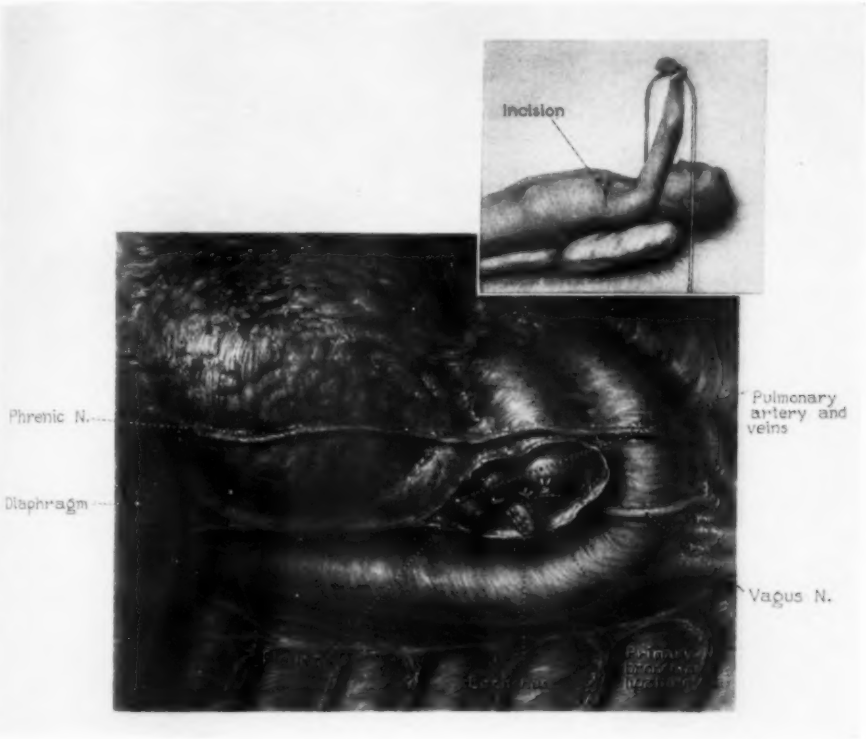

FIG. 7. In the *right upper corner* the position of the patient for left total pneumonectomy, is shown. In the *center* the amputated hilus of the lung is demonstrated. The ligated pulmonary artery and veins are visible above the bronchial stump. The primary encircling ligature of the bronchus may be seen proximal to the secondary suture line closing the amputated stump. In this patient the redundant mediastinal pleura was employed to close over the hilar structures. The proximity of the vagus and phrenic nerves is shown. The ease with which they may be exposed is evident.

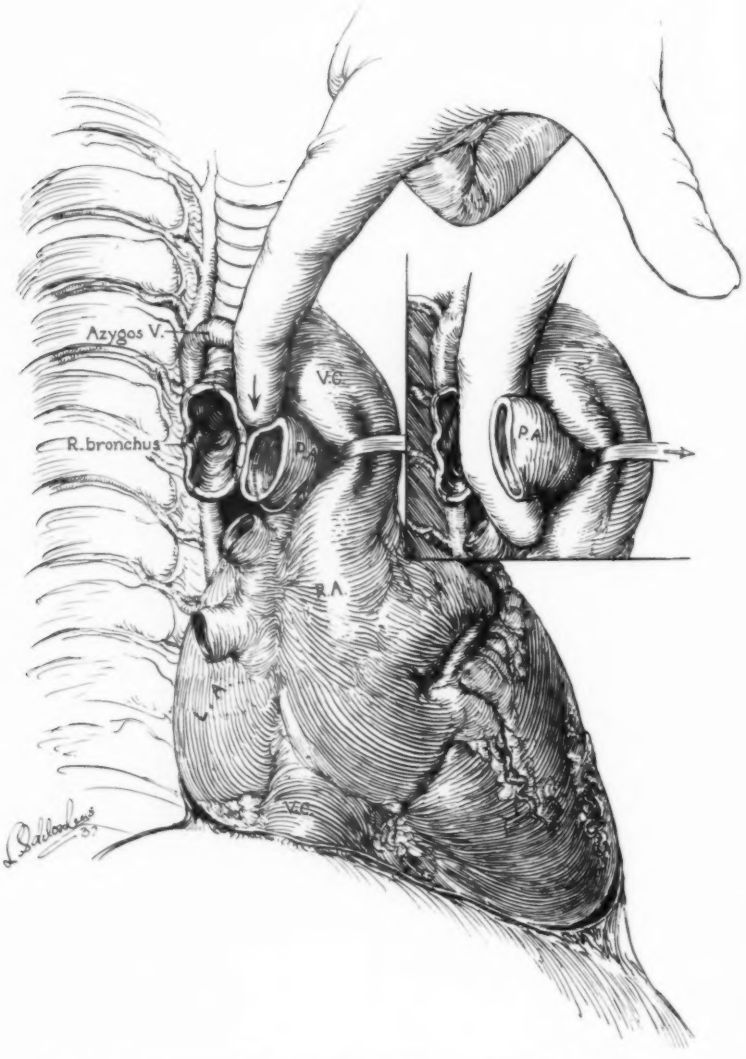

FIG. 8. DIAGRAMMATIC SKETCH DEMONSTRATING METHOD OF DISSECTING PULMONARY ARTERY FROM ANTERIOR SURFACE OF PRIMARY BRONCHUS

The anatomical relations of the primary bronchus and pulmonary artery are shown.

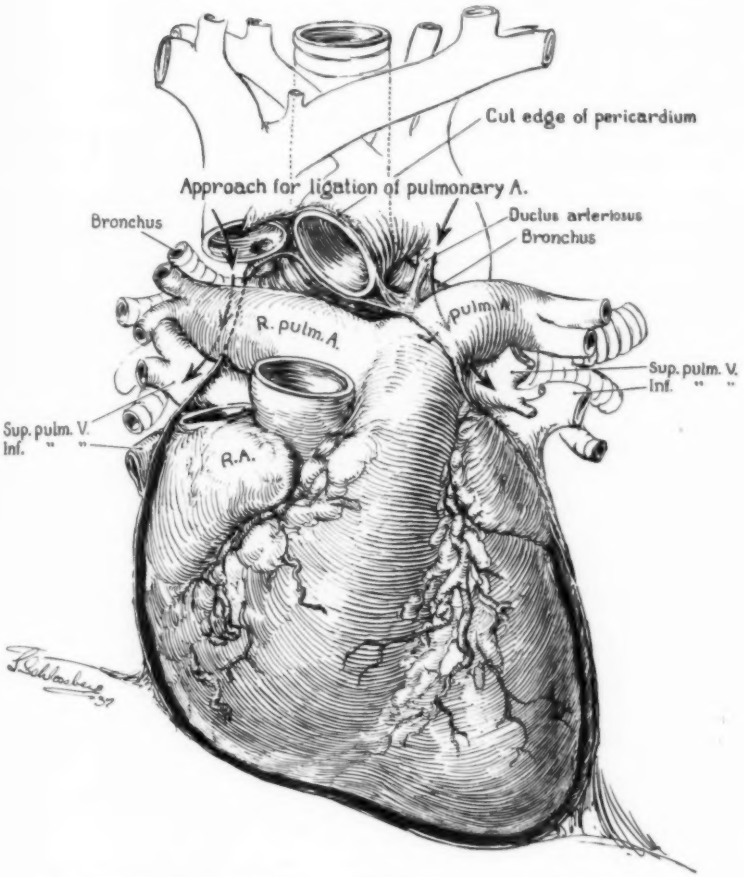

FIG. 9. DIAGRAMMATIC SKETCH TO DEMONSTRATE THE RELATION OF THE PULMONARY ARTERY TO THE REFLECTIONS OF THE PERICARDIAL SAC

The conus arteriosus and pulmonary aorta are within the pericardial sac, whereas the right and left pulmonary arteries run their entire course outside of and posterior to the pericardial sac. The right pulmonary artery is lower than the left.

about the bronchus high up, just distal to the bifurcation of the trachea (Figs. 4, 5 and 7). This ligature is firmly tied at once. Since it is placed around the primary bronchus near the bifurcation of the trachea above the point at which the bronchial artery applies itself to the posterior bronchial wall, no interference with the blood flow through the bronchial artery is incurred. This primary encircling ligature of the bronchus may be considered the second and the most important step in the operation of total pneumonectomy; the ligation of the pulmonary artery being the first. The pulmonary veins are then doubly ligated with medium "c" silk. If, however, the decision has been made to grade the operation into two or more stages then the ligatures may be placed only loosely about the veins and left untied, for the bronchial veins are of insufficient size to carry off from the lung the blood supplied by even the bronchial artery, or arteries, alone. If the flow of blood through the pulmonary veins, either the superior or inferior, is in any way interfered with, moist gangrene of the respective drainage bed will ensue, unless the lung is removed without delay. The ligation of the pulmonary veins may be considered the third step in the operation.

Amputation of the main bronchus just distal to the primary encircling ligature constitutes the fourth step in the operation. This step may be taken prior to the ligation of the pulmonary veins (step 3) if there is doubt about being able to complete the operation in one stage, for as mentioned above after ligation of the veins the operation must be completed. If the patient is in good condition, exposure for amputation of the bronchus is better when the veins are divided.

The object of the primary encircling ligature of the main bronchus is to occlude the lumen of the bronchus above the suture line at the cut end, and thus protect the latter from the pressure and strains resulting from respiration or coughing. This initial bronchial occlusion also prevents the collection, by gravitation, of infected mucus, pus or detritus in the blind pouch which abuts the inner side of the suture line. Amputation of the hilus of the lung is performed from above downwards on the left, and from below upwards on the right side. Only that portion of the vessels, pulmonary veins and artery, lying distal to the ligatures need be clamped. No lung or peribronchial tissue, or lymph glands should be left behind. If such is the case a complete pneumonectomy has not been performed.

The bronchus, whether it be the right or left, is cut across in the mediastinum not far from the bifurcation of the trachea and the primary encircling ligature (Figs. 5 and 7). The incision is made slightly obliquely to the long axis of the bronchus, on a line running from above and lateral, to below and medial. The cut edge of the stump forms an angle of about 45° with the superior border of the primary bronchus and of about 135° with its inferior medial border. In addition to the slanting direction of the incision across the bronchus, the cut is made on the bias so that the posterior membranous portion is a trifle longer than the more anterior cartilaginous wall. Interrupted fine "a" silk sutures are then placed in the membranous portion in such a way that the curved needle picks up a portion of the posterior membranous tissue a few millimeters proximal to the cut edge. The needle is then inserted into the cut edge of the mucous membrane and the cartilaginous ring of the bronchus directly opposite (Figs. 5 and 7). From ten to twelve of these sutures are laid in a fan-shaped pattern. Thus, when the knots are pulled home, the relaxed and relatively tough posterior membranous wall is not only snugly fitted to the inner surface of the semicircular cartilaginous ring at all points, but also, as a result of the way in which the sutures have been placed, the membranous portion is rolled over the cartilaginous cut edge in a way corresponding to the inversion of the intestinal wall. The cut ends of the mucous membrane are thus approximated on the inside of the blind-end stump. This method of closure of the cut end tends to flatten out the horse-shoe-shaped bronchial cartilage rather than constrict it and therefore no tension whatever is placed upon the suture line. Two parallel rows of through-and-through mattress sutures are placed proximal to the above-mentioned interrupted row. They are separated from the end and from each other by the width of one cartilaginous ring. The suture passes completely through the bronchial wall between the cartilaginous rings. These proximal sutures consist of no. 1 chromic catgut, because the latter would be less likely to cut through the posterior membranous layer than silk. Additional rows of these interrupted mattress sutures may be employed, whenever necessary. One row contains about eight sutures (Figs. 5 and 7).

The posterior membranous portion of the human bronchus is ample to line, as it were, the entire semicircle of the anterior cartilaginous

ring. Occasionally on the left side it may be helpful to leave a bit more of the under-lip of the membranous portion to curl back over the cut end. The membranous wall of the bronchus is abundantly supplied with blood by the bronchial artery.

A fact of some importance may be added. By the use of an oblique incision and a similar technique of closure, an adjacent portion of the trachea may be removed along with the involved bronchus, thus en-

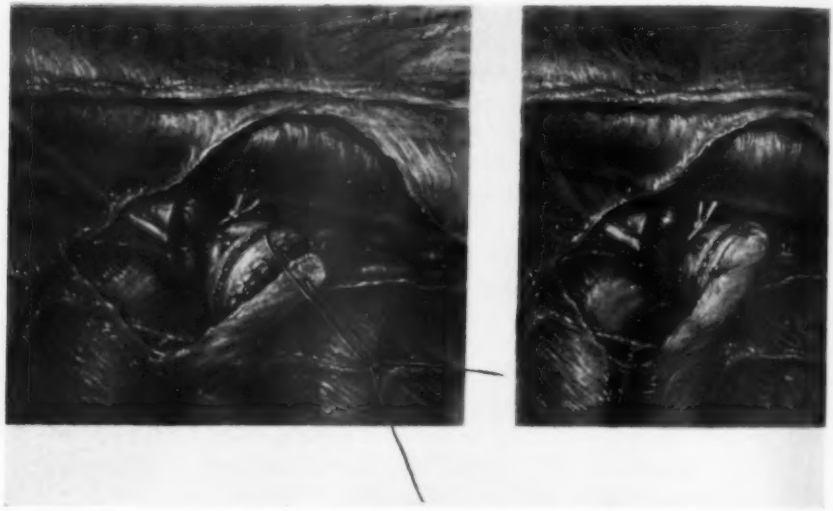

FIG. 10. USE OF PLEURAL PEDICLE FLAP TO COVER THE STUMP OF THE AMPUTATED BRONCHUS

In this drawing the stump of the right primary bronchus is being covered. The primary and secondary suture lines of the amputated stump together with the primary encircling ligature higher up on the bronchus, are shown.

abling the operator to deal with tumors extending as far as the carina or involving the lateral wall of the trachea.

After the suturing has been completed, it is well to cover over the stump of the bronchus with some available additional tissue (Fig. 10). A pedicle flap taken from the mediastinal pleura with some underlying areolar tissue, has been found available in many patients on either the right or left side. This flap may be slightly twisted or

reflected upon itself leaving the base attached in order to preserve its circulation. The free end may then be sutured to the bronchial stump. The division of the bronchus having been made high in the mediastinum, the stump is surrounded, while healing, with the more vigorous growth of the mediastinal areolar granulation tissue (Fig. 11). As an alternative, on the right side a small but sufficiently large

FIG. 11. Another method of using pleura to cover the proximal stump. In some patients the mediastinal pleura is so redundant that it is not necessary to cut the pedicle flap; in these cases the pleura may be sutured as shown in this drawing.

pedicle flap about 6 x 2.5 cm. has been cut away from the superior portion of the relaxed paralysed diaphragm which at the second stage operation will be found to lie almost against the bronchial stump. The tissue is sutured to the free end of the bronchus thus retaining its viability from the base through which it is normally attached to the diaphragm. On the left side, still other tissue is available in some cases; for example, the upper portion of the pericardial sac serves

adequately, but here too the diaphragm may be used. The procedure of supplementing the healing process of the bronchial stump by suturing to it some adjacent supporting tissue is a most valuable adjunct to insure primary and complete healing of the bronchus (Figs. 12 and 13).

Closure of the wound is accomplished by drawing the ribs together by means of a rib approximator (Fig. 14) which holds them in position while perichrondral sutures, usually three in number, of no. 10 braided silk are placed and tied. No attempt is made to suture the pleura or

FIG. 12. Following total left pneumonectomy in this case there was such an abundance of mediastinal pleura that complete covering of the hilar structures could be accomplished.

intercostal muscles. The regeneration of the former, and the healing of the latter require only a few weeks. The pectoral fascia is drawn together with interrupted medium silk while the skin is closed with fine silk (Fig. 15). It is usually necessary in the female to suture the breast subcutaneously, the latter serving as a good tampon over the pectoral fascia. Within two weeks the wound has healed solidly and there is no impulse or bulging during coughing. No drainage is employed. A rather snug dressing is applied and the patient is returned to the ward.

FIG. 13. Another example of the complete closure of the hilar structures following pneumonectomy, this time on the right side.

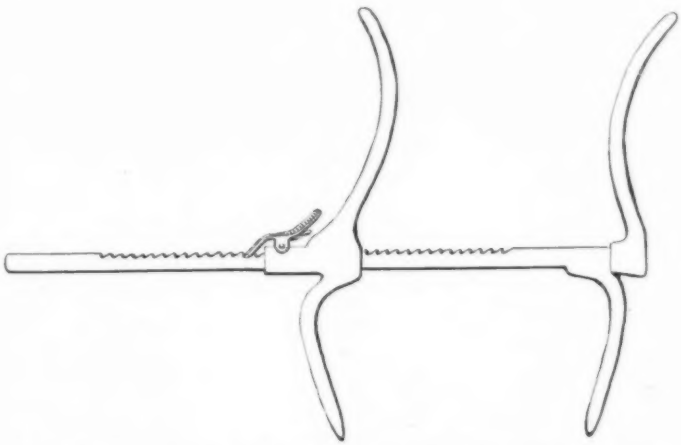

FIG. 14. INSTRUMENT USED FOR THE REAPPROXIMATION OF RIBS TO HOLD THEM IN PLACE WHILE THE PERICOSTAL SUTURES ARE TIED

The spike-like bits are inserted above and below the ribs to be approximated. They are then drawn together and held in position by means of the ratchet.

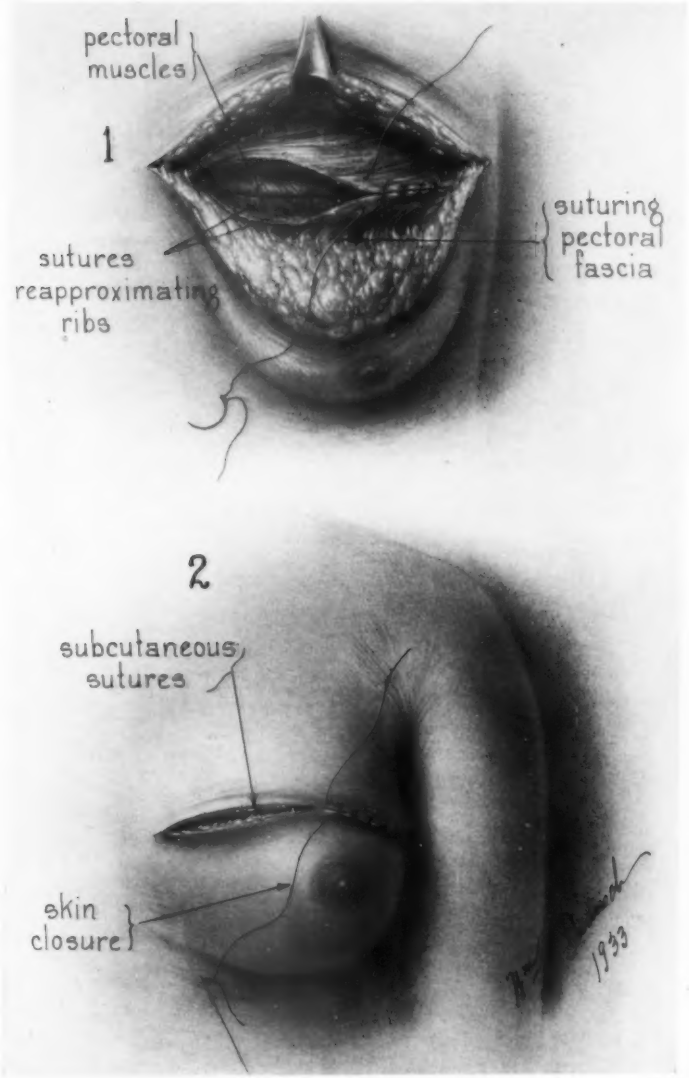
pectoral muscles
1
suturing pectoral fascia
sutures reapproximating ribs
2
subcutaneous sutures
skin closure
1933

FIG. 15

The patient's position in bed, postoperatively, should be flat with the foot of the bed elevated 6 inches in order that good tracheal drainage may be obtained. The patient is turned slightly upon the operated side so as to have the unaffected side free to expand, unhindered during inspiration. This position also promotes bronchial drainage from the unaffected side. An oxygen tent is used, if indicated. The intravenous administration of fluids is not employed except in unusual cases, in order to avoid undue strain upon the right side of the heart. (It is to be noted that the right ventricle is now functioning with only one pulmonary artery as an outlet.) Otherwise, the usual postoperative care is observed.

Following total pneumonectomy the inside of the thoracic cavity becomes completely lined with a surface of granulation tissue of considerable thickness. The size of the thoracic cavity is markedly reduced owing to various encroachments, namely, the elevation of the diaphragm, the shifting of the mediastinum toward the side of the operation, and the approximation of the ribs. In all instances, this decidedly shrunken cavity becomes filled with plasma which, in the absence of infection, will clot forming a coagulum into which fibrous connective tissue grows from the surrounding wall of granulation tissue. Between one and two weeks after pneumonectomy this once continuous cavity will have become transformed into a multilocular space consisting of walled-off pockets, the septa or walls of which are formed by the ingrowth of connective tissue. It is, therefore, inadvisable to drain the thoracic cavity after operation.

DISCUSSION

Owing to the location of the new growth and the extent of the disease in the majority of cases, total pneumonectomy is, except in most unusual instances, the ideal operation for the treatment of carcinoma of the lung. One-stage pneumonectomy is to be preferred when feasible but graded pneumonectomy should be employed whenever the slightest doubt arises regarding the patient's safety. The steps to be taken in carrying out either one-stage or graded pneumonectomy are identical and have been described. The operation may be interrupted following either the first or second step without jeopardizing the viability of the lung during the interval between

operations. In this manner the scope of usefulness of total pneumonectomy is sufficiently widened to deal with patients of various age groups and in different states of physical fitness. Any attempt to apply an inflexible operative routine in the treatment of patients differing in age, in constitutional symptoms and in extent of malignant disease will lead to difficulties and disappointments.

The series of successful total pneumonectomies herein reported may have been performed in a favorable group of cases, although the tumors in 90 per cent of them were considered large and extensive. The conclusion has been reached that when the new growth is confined to the lung and has not invaded the hilus or chest wall, total pneumonectomy carried out in accordance with the above described technique may be considered a procedure associated with a relatively low mortality. Seven consecutive cases, together with 13 additional cases in which this operation has been employed successfully would seem to be a sufficient number to justify this conclusion. In the operable cases the problem reduces itself solely to the dissection and ligation of the hilar structures. Occlusion of the pulmonary artery in the mediastinum renders haemostasis almost complete throughout the operation. Patience and knowledge of the anatomy of the hilus of the lung are all that are necessary to exercise complete control of these structures during the operation. The primary ligation and subsequent peripheral suture of the bronchus is no more than a routine procedure on a fixed anatomical structure, when the hilus is uninvolved. When the hilar structures are invaded the case should be considered inoperable and no attempt should be made to perform a total pneumonectomy. Those unusual instances of so-called "frozen lung" in which the lung is firmly fixed to the chest wall by dense adhesions, as well as those not infrequent patients in whom the growth has directly invaded the chest wall, should likewise be regarded as hopeless. Only those cases in which the lung is, in the main, free from the chest wall, and the hilus uninvaded, should be subjected to operation, otherwise a relatively safe surgical procedure will be brought into disrepute. Preoperative discrimination coupled with the tendency to grade the pneumonectomy, if indicated during the operation, will render the better results. Metastases to bronchial lymph glands offer less of a surgical problem than the dissection of

the axillary glands in the radical operation for carcinoma of the breast. The lymphatic glands along the primary bronchus and trachea are very easily seen owing to their pigmentation, and their removal offers no difficulty. There will, of course, always be some deaths from this operative procedure as from all others, but the mortality should be unassociated with any technical defects in dealing with the pulmonary vessels or bronchus if these structures have been individually ligated, step by step.

When an encircling ligature is placed around the primary bronchus and then tightened to the maximum of one's ability, the lumen is occluded mainly by the infolding of the posterior membraneous portion containing the bronchial artery or arteries. Owing to this fact, the bronchial artery remains patent and the circulation to the distal stump of the amputated bronchus, if the pneumonectomy has been performed in one stage, or to the lung if the pneumonectomy has been graded, is sufficient to maintain viability of the stump (Figs. 16 and 17).

Wood and Miller (5) observed variations in the number and size of the bronchial arteries, depending upon certain pathological changes in the lung. It was noted that the number and size of the bronchial arteries increases in carcinoma of the lung probably because of the greater nutritional demands of the tumor. It has also been our clinical observation that the size of the pulmonary artery decreases in direct proportion to the extent of involvement of the lung by the tumor. The less the aerating ability of the lung parenchyma, the less blood will be carried by the pulmonary artery for oxygenation, and, conversely, the more will be supplied by the bronchial arteries for maintenance of nutrition.

It is interesting to note, in reviewing the literature on closure of the primary bronchus that as long ago as 1909 Halsted (6) suggested closing the bronchus with interrupted silk sutures and reported the results of his experiments before the American Surgical Association. In 1920 Heuer and Dunn (7) called attention to the efficacy of a simple transfixion ligature of the primary bronchus in dogs and made comparative experiments with the other more complicated methods which had previously been reported. They concluded that the simple transfixion ligature for closure of the bronchus was to be preferred. Because of the sterility of the dog's bronchus, they expressed

FIG. 16. LIPIODAL BRONCHOGRAMS FOLLOWING LEFT AND RIGHT TOTAL PNEUMONECTOMY

In the upper photograph the stump of the left bronchus is outlined by a thin pool of lipiodal. In the lower the right primary bronchus is likewise shown. The close proximity of the occlusion of the primary bronchi to the bifurcation of the trachea is evident. The lipiodal is pooled at the site of the primary encircling bronchial ligature.

the fear that the presence of infection in man would interfere with the healing of the bronchus *per primum*. In this entire series of cases of carcinoma of the lung, the primary bronchus on the affected side contained various organisms, but in spite of the presence of infection, primary healing of the bronchus has been secured in every case. The previous experimental observations of Halsted and Heuer have thus been confirmed in human subjects. It is therefore felt that of the various methods of closure of the primary bronchus which have been employed in our cases of carcinoma of the lung, the technique

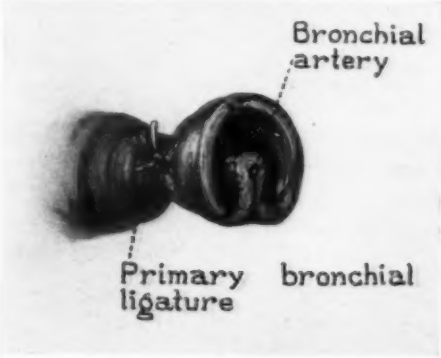

FIG. 17. DIAGRAMMATIC DRAWING ILLUSTRATING THE EFFECT OF A CIRCUMFERENTIAL LIGATURE OF THE BRONCHUS

The primary encircling ligature produces an infolding of the posterior membranous portion. In some instances the latter is so abundant that the degree of compression demonstrated in this drawing under the encircling ligature, cannot always be obtained.

herein described is superior to other methods. Great care should be exercised in the closure of the bronchial stump and the placing of the sutures therein, but the keystone to secure occlusion of the bronchus and its subsequent healing, and likewise to the success of total pneumonectomy, would seem to be the *primary encircling ligature placed around the primary bronchus just distal to the bifurcation of the trachea.*

Figures 1 and 15 of this article appeared in an earlier publication (3). They are reproduced here with the permission of the editor of *The Journal of the American Medical Association.*

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STUDIES ON HYPERSENSITIVITY TO CATGUT AS A FACTOR IN WOUND DISRUPTION

KENNETH L. PICKRELL, M.D.

From the Department of Pathology, and Bacteriology The Johns Hopkins University and Hospital

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The catgut suture is the evolution of the musical string. Made from linen, animal skins, sinews and intestines, they were used for sewing, tying, mending and for musical instruments. Strings from the harp and violin, which were made from the twisted intestines of sheep and other animals, appear in the records of surgery throughout the ages. The Arabian Rhazes (900 A.D.) describes the stitching of wounds with a thread made from the intestines of sheep (1). In the next century, Albucasis sutured with a thread made from the intestines of sheep. Celsus, in the first century A.D., describes the ligature as of ancient origin. Galen (2) in the second century described the use of catgut (*graciles chordae*), silk and hemp. In 1816, Physick (3) demonstrated the absorbability of catgut and the non-absorbability of flax and silk, and this was confirmed in 1864 by Porta (4). Despite these scattered early experiments, research in the field really began with Lister (5), who in 1869 first referred to the use of antiseptic catgut. With his work there was initiated a tremendous interest in surgical suture material which has extended down to the present time.

Catgut consists of the submucosa of the small intestine of sheep. In its manufacture, the intestine is split longitudinally, usually into three strips. The mucosa is scraped off from the inner side, then the serosa and the two muscular layers are scraped off from the outer side, thus leaving only the submucosa. The strips of submucosa are subjected to alkaline baths for the purpose of neutralizing any acid or toxic substance which may have been embedded in them as a result of the digestive process. The strips of submucosa are then spun into a cord called *catgut* which is essentially collagen. According to Bodansky (6), connective tissue contains about 60 per cent water and 40

per cent solids. Of the latter, about 0.5 per cent consists of inorganic matter. The principal organic constituent of fibrous tissue is the albuminoid, collagen, which composes about 32 per cent of the tissue, the remainder being made of elastin, an albuminoid, ether soluble lipids and nonprotein constituents.

PREVIOUS INVESTIGATIONS

In studying the relationship of suture material to the healing of wounds and the mechanism of postoperative wound disruption, several factors have received serious consideration. The most recent of these being the possibility of catgut allergy. The question of allergic manifestations to catgut has presupposed that individuals might be rendered sensitive to catgut through parenteral deposit of the material in the course of an earlier operation or through previous treatment with sheep serum.

Reil (7), who studied the mechanism of catgut absorption from both a physiological and a chemical point of view, states that in the condition in which catgut is at the time of its introduction into the tissues it can neither be absorbed nor serve as an antigenic irritant, because the proteins contained in it are in an insoluble form. The absorption of catgut proceeds through the agency of the leucocytes. Their tryptic and eryptic ferments split the proteins in succession to peptones, polypeptides and amino acids. Reil states that "because the cleavage products with large molecules are at once further decomposed all possibility of irritation of antigenic origin may be dismissed." There is, however, no evidence that catgut is more promptly and completely decomposed than are other foreign proteins which do incite hypersensitivity.

Frugoni (8), on the basis of chemical analyses, states that the substances present in a saline extract of catgut are not albumins but albumoses which are without antigenic power and, therefore, incapable of causing sensitization.

Marchesani's experiments (9) indicate that no specificity exists between sheep serum and catgut, but his results were discordant, for he reports that strands of catgut buried intradermally in guinea pigs sensitized to sheep serum, caused in some cases a greater leucocytic response than in normal guinea pigs.

Gratia and Gilson (10) state that fragments of catgut, either plain or iodated, placed intraperitoneally in guinea pigs previously sensitized to horse serum or sheep serum or both, caused local edema and hemorrhage. They interpret this as the Arthus phenomenon and suggest that it may be a cause of postoperative adhesions. The same result was obtained in rabbits sensitized to either horse serum or sheep serum and later injected intraperitoneally with an emulsion of powdered catgut. The authors do not comment on the anomalous fact that the animals sensitized with catgut reacted equally to horse and to sheep serum—a matter on which Bruynoge commented in his discussion of the paper. In the authors' reply it is still difficult to determine whether they intended to state that the sensitivity to catgut was nonspecific. Frugoni (8) was unable to verify the occurrence of this reaction, either macroscopically or microscopically.

Moriconi (11) was unable to demonstrate precipitin to extracts of catgut in the serum of rabbits that had been subjected to the absorption of either plain or iodated catgut. Neither was he able to produce any symptoms of general or cutaneous sensitivity in rabbits subjected to the repeated absorption of catgut.

Frugoni (8) was unable to demonstrate any changes in the serum of rabbits that had received catgut extract intravenously or catgut implanted intraperitoneally. Precipitin tests were entirely negative. Attempts to produce anaphylactic shock in guinea pigs that were sensitized with sheep serum and then injected intravenously with catgut extract were likewise negative, as had been shown previously by Moriconi (11). Attempts to produce anaphylactic shock by the intravenous injection of sheep serum in guinea pigs that had catgut implanted in the peritoneal cavity 60 days previously were completely unsuccessful. Frugoni obtained identical local reactions, both macroscopically and microscopically, when catgut was implanted intraperitoneally in control rabbits, in rabbits sensitized with sheep serum, and those previously treated with catgut. The wounds healed *per primum* and there was no increased local reaction.

Tripp (12) reports the case of a patient who developed asthma while convalescing from a second operation in which chromic catgut had been used. It is not stated what suture material had been employed in the first operation five years previously. The asthma, however,

totally disappeared after a few weeks. He reports this as a case of catgut sensitivity, but no tests were made to confirm his assumption.

Kraissl (13) states, "It is possible to sensitize guinea pigs to catgut and to produce disruptions of laparotomies sutured with this material." Guinea pigs were used because "rabbits are rather difficult to sensitize." It is a well-known fact that tissue sensitivity to foreign animal protein can be produced more easily in rabbits than in other laboratory animals. On the other hand, typical anaphylactic shock can be readily induced in the guinea pig. In Kraissl's experiments, "19 guinea pigs were sensitized with plain and chromic catgut. This was done with intraperitoneal injections of a colloidal suspension, by burying catgut itself subcutaneously, and by closing abdominal laparotomies with catgut. In addition, one was sensitized by intracardiac injection and another by repeated intradermal injections." Intradermal injections of approximately 0.1 cc. of catgut extract, containing 0.13 mg. total nitrogen per 100 cc., were used to determine sensitivity. Only three had positive skin tests. Data are lacking describing the appearance of a positive test. In all of the "sensitized" animals laparotomy incisions were subsequently made. These incisions were closed with through and through bolt sutures of plain or chromic catgut. No statement is made regarding the length of time between the primary introduction of catgut and the test laparotomy and suture. Five incisions disrupted between the second and fourth postoperative days, and one on the eighth postoperative day. In addition, 4 incisions healed abnormally. None of the incisions in 6 control guinea pigs disrupted, but one healed abnormally.

In regard to these experiments of Kraissl (13), several points may be raised. No mention is made of any aseptic technic employed during the execution of the laparotomies. That the incisions may have been infected is suggested from the photographs which are submitted as evidence of disruption, for the operative sites do not appear to have been carefully prepared. Even in cases in which disruption occurred on the fourth postoperative day the operative site shows long hairs. No attempt was made to demonstrate sensitivity by the production of anaphylactic shock in the "sensitized" animals, nor were any serologic tests performed to test for the formation of precipitins (14).

In a later study (15), which includes the experiment previously

described, Kraissl and Kesten found that of 28 guinea pigs "sensitized" to plain catgut, 10 disrupted their incisions.

EXPERIMENTAL STUDIES

The present experiments were carried out in order to determine whether domestic catgut could incite hypersensitivity, either general or local, in either rabbits or guinea pigs. It was decided at the outset to use a standard brand of boilable catgut, selected at random from the surgical supply rooms of the Johns Hopkins Hospital.

Sixty rabbits and 80 guinea pigs have been used in the experiments here reported. In the first experiment, 12 guinea pigs were subjected to six implants of plain catgut at intervals of one month. The procedure was as follows: The day prior to operation the entire abdomen and flanks of the animal were clipped and shaved. Under ether anesthesia, a wide operative field was cleaned with ether, iodine and alcohol; after which the operative field was appropriately draped with sterile towels. Rigid asepsis was observed throughout. The instruments and ampules of catgut were sterilized by boiling for 10 minutes. A paramedian incision about 4 cm. in length was made through the skin and subcutaneous tissue. The muscle was then divided by blunt dissection, and the peritoneum opened the full length of the incision. The catgut before use was softened in sterile physiological salt solution. A continuous suture of plain number 0 catgut was used to close the peritoneum. Interrupted sutures of number 0 catgut were used to close the muscle and skin respectively. Square knots were tied and cut moderately close. Every effort was made to reproduce the technic employed in the operating room, except for the fact that no gauze dressing was applied over the incision. Occasionally, however, the incision was sealed with collodion. One month later, the same process was repeated, using the back of the animal. Here likewise a paramedian incision was made, and carried down through the heavy musculature of the back. The muscle and fascia were approximated with interrupted sutures of plain number 0 catgut, the skin edges being approximated with interrupted sutures of the same material. This process was repeated on six occasions at intervals of one month, alternating the abdomen with the back for the operative site.

The second experiment, using 12 rabbits and 12 guinea pigs was

similar to the one above except for the fact that number 0 chromic catgut was employed.

Lest it should be said that an insufficient quantity of catgut had been implanted by means of the sutures in the previous experiments, even though an amount equivalent to that employed in routine surgical procedures was used, a third experiment was performed in which, instead of simply making incisions and closing them with plain or chromic catgut, two or three strands of catgut 3 to 4 cm. in length were buried either intramuscularly in the back or subcutaneously in the abdominal wall. In 6 rabbits and 6 guinea pigs, two or three strands of plain number 1 catgut were buried on six occasions at intervals of one month beginning with the back and alternating with the abdomen. The incisions were closed with number 0 plain catgut. A similar number of animals were subjected to the absorption of two or three strands of number 1 chromic catgut at intervals of 30 days on 6 successive occasions. The incisions were closed with chromic catgut in the manner previously outlined. When plain catgut was buried, plain catgut was used to close the wounds; and when chromic catgut was buried, chromic catgut was used to close the wounds.

The incisions were examined carefully every day from the beginning. In both rabbits and guinea pigs, whether plain or chromic catgut was used, the incision in every instance healed *per primum* following each operation. There was no evidence whatever of any increased local reaction in the treated animals as compared with normals. There were no disruptions, no infections and no evidence of either local or general sensitivity. Prior to each operation in the rabbits, precipitin tests for antibody production were carried out. In addition, intradermal tests in both rabbits and guinea pigs were performed, by injecting 0.1 cc. of a catgut extract.[1] These, also, were completely negative.

[1] The catgut extract was made in the following manner: 15 skeins of the number 3 plain catgut were pulverized by grinding in an Arabian coffee-grinder. After placing the catgut powder in a heavy liter bottle, 500 cc. of sterile physiological saline and pyrex chips were added. The container was then placed in a mechanical shaker for 12 hours. This yields a colloidal suspension of catgut particles in a saline vehicle. The supernatant fluid was then placed in a vacuum dryer. 0.1 gram of the powder thus obtained was placed in glass ampules,

In another experiment, 3 rabbits had 2 strands of purified catgut[2] implanted intramuscularly in the back on three occasions at intervals of one month; 3 rabbits had 10 to 12 grains of powdered purified catgut deposited in the peritoneal cavity on three occasions at monthly intervals through an incision 4 to 5 cm. in length; 3 had 10 to 12 grains of powdered commercial plain catgut implanted in a similar manner; 3 had 10 to 12 grains of powdered chromic catgut implanted intraperitoneally; 3 had a skein of plain number 0 catgut buried intraperitoneally on three successive months; and 3 had a skein of number 0 chromic catgut implanted intraperitoneally on three occasions. In each instance, the incision was closed in layers with number 0 catgut of the type implanted.

Never was there any evidence of either local or general reaction, and the incisions in each instance healed *per primum*. It was interesting to find that at the end of a month no catgut could be found even in histological sections, regardless of the form in which it was deposited. Inasmuch as no trace of the catgut could be found after one month, the peritoneal cavities were examined thereafter in 7 to 12 days after the second catgut implant. At this time the powdered catgut could be recognized as minute flecks on the surface of the intestine which was slightly reddened. The reaction, however, was no more marked than that found in three similarly treated control animals. The rabbits in which the skein of catgut had been deposited, either plain or chromic, showed even less reaction, limited to the immediate vicinity of the catgut implant, i.e., either between loops of small intestine or in the gastrocolic ligament. The plain catgut was found as a mass of

covered with xylene and the ampules sealed in a flame. The tubes were then sterilized under oil for one hour. This is the process generally employed by manufacturers in the sterilization of catgut. Using sterile technic, the tops of the ampules were then removed and a cotton plug inserted, thus allowing the xylene to evaporate. This completed, 5 cc. of sterile physiological saline were added to each tube. This will dissolve the greater portion of the catgut powder. The resulting clear, sterile supernatant fluid was then withdrawn and placed in sterile serum bottles or tubes. Total nitrogen determinations revealed not less than 50 mg. per 100 cc. as determined by the micro-Kjeldahl method.

Less concentrated alkaline extracts were prepared using the method of Kraissl (13).

[2] The purified catgut was kindly furnished by Davis & Geck, Inc.

rather friable white material, while the contour of the chromic skeins was still well differentiated, and the strands still bore considerable tensile strength. By the end of the third week, only traces of the powdered catgut could be found between loops of adherent intestine and there was no longer any reaction whatever. It should be made clear that there were no adhesions but simply a coherence between adjacent loops of intestine, limited only to the site of the catgut implant. The skeins of plain catgut presented the same appearance except for being considerably smaller in size than after the second week. The chromic catgut skeins at the end of the third week appeared as a mass of friable white material. And as was previously stated, at the end of four weeks, no trace whatever of the plain catgut could be found, while in 4 instances remnants of chromic catgut skeins were recognized as small, white friable masses.

One month after the third deposit of catgut, the peritoneal cavities were again examined. Numerous friable adhesions between adjacent loops of bowel were found limited to the site of the catgut deposits. Precipitin tests performed at monthly intervals on the serum of the rabbits for antibody production were entirely negative. Intradermal tests for local sensitivity as described above were negative.

To test for anaphylaxis 42 guinea pigs were used. 12 were injected intravenously into the jugular vein with 1 cc. of our catgut extract; 12 were injected intravenously with 1 cc. of Kraissl's extract of plain catgut[3]; and 12 were injected intravenously with 1 cc. of Kraissl's chromic catgut extract[3]; 6 guinea pigs were used as controls in which saline was injected. After three to four weeks, all animals were again injected intravenously with 1 cc. of the prescribed extract. Not a single reaction was encountered. The intravenous injections were made into the jugular vein without anesthesia.

To determine conclusively whether any increased local reaction occurred around a single intradermal strand of catgut in animals submitted to the previous absorption of catgut, either plain or chromic, 6 rabbits and 6 guinea pigs had laparotomies performed and two or three strands of number 0 plain catgut buried subcutaneously or intramuscularly. The incisions were closed in layers using number 0 plain catgut. 6 rabbits and 6 guinea pigs were similarly treated burying

[3] Extracts kindly furnished by Dr. C. J. Kraissl.

two or three strands of number 0 chromic catgut. 3 rabbits and 3 guinea pigs were injected intravenously with 1 cc. of our catgut extract, and an equal number of animals were injected with 1 cc. of Kraissl's extracts.[3] After one month, using rigid asepsis, a strand of either number 0 or number 00 catgut about 2 cm. in length was inserted intracutaneously, using an atraumatic needle, in each flank. In those animals in which plain catgut had been previously buried, the endermal implant was likewise of plain catgut; and when chromic catgut had been buried, the implant was of chromic catgut. The sites of implant were observed macroscopically, and at the end of 24 and 48 hours respectively, sections of skin containing the catgut implant were removed for microscopic study. The same procedure was performed on 6 normal rabbits and 6 normal guinea pigs.

The site of the catgut implant was always discernible macroscopically as a small erythematous streak. Never was there any greater reaction in those animals that had previously been treated with catgut as compared with similarly treated controls. Microscopic sections revealed a local accumulation of leucocytes in both the previously treated and the normal animals, but in no instance was the leucocytic emigration greater in either the rabbits or the guinea pigs which had been previously treated with catgut, than in normal control animals.

CLINICAL STUDIES

Only three cases of disruption of surgical incisions in which catgut had been used have occurred on the surgical services of the Johns Hopkins Hospital during the past two years. During this period approximately four thousand incisions have been closed with catgut. We have had an opportunity on these three occasions to test for local sensitivity immediately following disruption. Each patient was injected intradermally on the volar surface of the forearm with 0.1 cc. of our catgut extract, with a normal saline control, and in addition, with 0.1 cc. of Kraissl's plain and chromic extracts. Similar quantities of extract diluted 1 to 10 were injected intracutaneously in the opposite arm. The tests, performed immediately after a complete disruption, were negative. Furthermore, we have tested one hundred patients preoperatively and postoperatively in a similar manner, likewise with negative results. The sites of inoculation were observed

constantly for one hour and at daily intervals for several days. These same patients were again tested three to four weeks after operation, when it was assumed that the greater part of the catgut had been absorbed. The tests were completely negative.

DISCUSSION

It has been stated (13) that "it is possible to sensitize guinea pigs to catgut and to produce disruptions of laparotomies with this material." We have been unable to confirm that conclusion. In these studies we have been unable to demonstrate any evidence of either local or general hypersensitivity to catgut or extracts of catgut in laboratory animals subjected to either a single or repeated absorptions of catgut. In addition, all attempts to produce anaphylaxis in guinea pigs that had catgut buried or that had been injected with 1 cc. of catgut extract one month before a second occasion with a similar quantity, were unsuccessful.

The present experiments, together with the clinical studies presented above, lead us to believe that wound disruption will rarely occur if aseptic precautions are properly observed, unless there are predisposing complications such as (1) insecure closure of the wound, (2) cachexia and decrepitude occurring in patients mainly in the fifth, sixth and seventh decades affected with malignant tumors and debilitating disease, and (3) increased intra-abdominal pressure (either of the constant type resulting from ileus, or more especially from the violent, explosive type caused by vomiting, retching, straining, hiccoughing, coughing, sneezing, etc.).

It is in no sense the intent of the present paper to imply that catgut should be used in preference to silk as a suture material. The experiments bear simply on the question of hypersensitivity to catgut and they indicate that the use of catgut carries no danger referable to hypersensitivity to this material.

SUMMARY

1. It has been impossible in the present experiments to sensitize either guinea pigs or rabbits to commercial catgut or to an extract from catgut.

2. No evidence of either local sensitivity or general reactions could

be elicited in guinea pigs or rabbits subjected to the previous absorption of catgut.

3. It was not possible by the intravenous injection of a catgut extract to produce anaphylactic shock in guinea pigs that had been previously treated with either catgut or catgut extract.

4. Serologic tests for antibody production in animals treated with catgut were negative.

5. No wound disruptions occurred in either rabbits or guinea pigs which had been previously treated with catgut when proper aseptic precautions were observed.

6. Although catgut implanted intradermally in both rabbits and guinea pigs caused an inflammatory response, the leucocytic emigration was no greater in those animals that had been previously treated with catgut or catgut extract.

7. In the human being no evidence of sensitivity could be demonstrated following the disruption of three surgical incisions that had been closed with catgut. In 100 clinical cases in which catgut had been used, tests for sensitivity to catgut extract were carried out preoperatively and then one month following operation. In no case was sensitivity demonstrable.

8. One can finally conclude that although catgut, like any other suture material, acts as a foreign body and causes a slight leucocytic response, it does not act as an antigen to induce the hypersensitive state.

The author deeply appreciates the generous advice and assistance of Dr. Arnold R. Rich.

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BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Surgical Pathology. By WILLIAM BOYD. 4th ed. revised. 886 pp. Illus. $10.00. (*W. B. Saunders Company, Philadelphia, 1938.*)

This text-book of pathology places emphasis on certain aspects of the subject which are of importance to the surgeon. For those surgeons and surgical pathologists who desire to have a treatise which will give in detail the anatomical and physiological changes in the tissues, the book cannot be recommended. Too little emphasis is placed upon certain important tissues. For example, only 29 pages are devoted to a discussion of the pathological alterations in lymph nodes. In this day of biopsies certainly more stress might have been placed upon this phase of surgical pathology. There is no discussion of the bone marrow in disease. Certainly also, a single page is too little to devote to the subject of the physiology of intestinal obstruction, so important to every surgeon.

R. H. F. JR.

Pathological Technique. By FRANK BURR MALLORY. 434 pp. Illus. $4.50. (*W. B. Saunders Company, Philadelphia, 1938.*)

In preparing this work the author stresses that he has strived "to retain the best of the past and to add only the most promising methods of the present." This he has certainly succeeded in doing. The book contains such a wealth of information that it should prove invaluable to every pathologist.

R. H. F. JR.

Syphilis, gonorrhea and the public health. By NELS A. NELSON, M.D., AND GLADYS L. CRAIN, R.N. 359 pages, $3.00. (*The Macmillan Company, New York, 1938.*)

Even before the recent nation-wide revival of interest in the venereal diseases, there were a few states, notably New York and Massachusetts, which had comprehensive programs looking toward the control of syphilis. It is of considerable value, therefore, to have available at the present time, a book on this subject written by the Director and Epidemiologist, respectively, of the Division of Genito-infectious Diseases of the Massachusetts Department of Public Health.

The first part of the book is devoted to a discussion of the clinical and therapeutic aspects of syphilis and gonorrhea, and to a presentation of statistics bearing

on the prevalence and distribution of these diseases. These chapters are not exceptional and form little more than a background for that which follows.

The second half of the book, together with the two opening chapters on attitudes and approaches, contains exceedingly interesting and valuable material. The peculiar nature of the diseases themselves and the influence of these peculiarities upon control procedures are recognized. Various phases of the program, such as laws and regulations, case finding, treatment facilities, laboratory and consultation services, and prophylaxis are discussed in detail. Useful chapters on costs and budgets are included.

It is interesting to note, in view of the authors' wide experience, the insistence with which they urge that the program can be made effective with a minimum of legal regulation.

T. B. T.

Treatment in General Practice. By HARRY BECKMAN. 3rd ed. 787 pp. $10.00. (*W. B. Saunders Company, Philadelphia, 1938.*)

This is an excellent book. I intended to skip through it for purpose of review, but I find that I read the book in its entirety, for its concise but accurate descriptions of disease, and its excellent therapeutic regimens. Textbooks on treatment are often uncritically inclusive, but here there is a display of healthy, good-natured skepticism and mature agnosticism. This makes a text which is particularly valuable to the medical student.

S. W.

Laboratory Manual of Hematologic Technic. By REGENA COOK BECK. 389 pp. Illus. $4.00. (*W. B. Saunders Company, Philadelphia, 1938.*)

This work is designed particularly for the training of the technician. Each chapter ends with a list of terms to be learned and a series of review questions. The methods described have been chosen according to the views or habit of the author, no attempt being made to include all existing methods. The style is clear and didactic. There are 79 figures, all in black and white.

The author expresses a desire to place emphasis on technic and commendably refers to the need for correct technic. In the opinion of the reviewer, this important feature of a book for technicians might have been emphasized more than it is. In some instances, such as in the description of the Van Allen hematocrit and the method for total blood volume estimation, there is no mention of sources of error. It is unfortunate also, since the choice of methods is arbitrary, that references are not given for other commonly used procedures. A selected bibliography would also be useful.

A surprising statement in this book is that differential counts on blood films made on cover glasses are not accurate unless 8,000 to 30,000 leukocytes are classified. The author considers a differential count of 100 cells in a blood film made on a slide to be the preferable procedure!

M. M. W.

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS. 2nd ed. 1413 pp. Illus. $12.50. C. V. Mosby Company, St. Louis, 1938.

There is no need for an extended note on the appearance of the Second Edition of this excellent text-book, as the previous Edition was reviewed in a recent number of this journal. Some of the irregularities noted in the earlier review have been smoothed out. The book can be recommended highly, particularly to the man who is interested in the physiologic bases of disease as well as in the immediate care of the patient.

J. T. K.

Pneumonia and Serum Therapy. By FREDERICK T. LORD AND RODERICK HEFFRON. Revised edition of Lobar Pneumonia and Serum Therapy. 148 pp. $1.00. The Commonwealth Fund, New York, 1938.

Under the auspices of the Commonwealth Fund, Lord and Heffron, in 1936, published the results of their studies on horse serum therapy in pneumococcus pneumonia. The extension of the use of therapeutic horse sera to types other than I and II and the introduction of rabbit serum have necessitated a revision of their first edition. The second edition, in 1938, contains a discussion of the horse serum treatment of Types I, II, V, VII, VIII, and XIV, as well as a consideration of the present status of anti-pneumococcic rabbit serum.

The handbook discusses briefly certain of the features of pneumococcic pneumonia pertinent to the clinical and bacteriological diagnosis, to recovery and to the selection of cases for serum treatment. A scheme for the testing of serum sensitivity and an outline for serum administration are given. A chapter is devoted to serum reactions and their treatment. Lastly, Lord and Heffron present the results of serum therapy from their collected cases in Massachusetts and compare these with the reports of other authors.

The authors have limited the contents of their book to the features of pneumococcic pneumonia concerned with serum therapy and it is for this reason that the book is valuable. In brief and readable form one may readily become acquainted with the present concept, theoretical and practical, of the serum treatment of pneumonia.

R. C. T.

The Pneumonias. By HOBART A. REIMANN. 381 pp. Illus. $5.50. W. B. Saunders Company, Philadelphia, 1938.

Reimann's book is well written and readable. It is a text covering briefly the biology of the pneumococcus, the etiology and pathology of lobar pneumonia and the clinical features of this disease. The more common pneumococcus types are considered as specific pneumonias. Moreover, while the pneumococcus holds the most prominent place in the book, the author also discusses the other etiological agents of pneumonia, namely the various cocci and bacilli, the filtrable viruses and fungi, and gives attention to pneumonia as a part of systemic diseases.

Certain criticisms may be advanced against the book. It is brief and the

reader will gain little more than a bird's-eye view of the various features of the disease. The author covers old territory in the customary text-book fashion, adds nothing new, and what he has to say is familiar to those who have an especial interest in pneumonia work. The failure of the author to include his own clinical material detracts from the value of his book. With little extra labor, he could have enlarged the very meagre and inadequate bibliography and thereby enhanced the book's usefulness.

The chief merit of Reimann's book lies in the author's concise and good style. It is recommended to the medical student who has a beginning interest in pneumonia or to the practitioner who has a limited time to spend in bringing up to date his knowledge of the subject.

R. C. T.

Survey of Chronic Rheumatic Diseases. Contributed by contemporary authorities in commemoration of the bicentenary of the Royal National Hospital for Rheumatic Diseases, Bath, 1738–1938. 336 pp. Illus. $6.50. Oxford University Press, New York and London, 1938. (Oxford Medical Publications.)

The book serves admirably its purpose as stated in its foreword. The History of Chronic Rheumatism is a fitting introduction to such a commemorative volume and gives the background we so often overlook in the study of disease. Chronic rheumatism lends itself in an unusual way to such treatment, and the author unfolds its history in not only an interesting but scholarly manner.

The presentation of the knowledge thus far acquired concerning chronic rheumatism offers many difficulties. So much work has been done on this problem and so many divergent opinions are held and stoutly defended that it is difficult to properly evaluate the data accumulated. The approach offered in this volume is a particularly pleasing one. Dealing with the controversial phases separately permits the reader to focus his attention and greatly lessens the distraction which difference of opinion engenders. In the discussion of the various aspects of rheumatic disease the authors have been careful to present the subject matter in an unbiased fashion, seeming always to be mindful of its unsettled state, thus allowing the reader to weigh the evidence for himself. Particularly is this true of the chapter, "Is Rheumatoid (Atrophic) Arthritis a disease of Microbic Origin." Here the author carefully presents the evidence both for and against this view, and then has the courage to express his personal conclusions from the argument. Such analysis of data is stimulating and such forthrightness praiseworthy.

The review conveys to the reader the complexity of the problem, the interrelation of its many phases and a better appreciation of the difficulties to be surmounted in its solution. It presents the vast amount of work done on the subject in a concise manner and should be genuinely stimulating to all who read it.

C. W. W.

Spinal Anaesthesia. By LOUIS H. MAXSON. 409 pp. Illus. $6.50. J. B. Lippincott Co. Philadelphia, 1938.

This is a book for which there is, in the reviewer's opinion, a definite need. The literature on spinal anaesthesia is voluminous and is filled with reports enthusiastically either advocating or condemning the procedure. Too often these writers have become advocators or prosecutors, and too rarely impartial observers.

Doctor Maxson has presented and assorted all the available knowledge on the subject, including evidence both favorable and unfavorable. It is true that the reader receives the definite impression that spinal anaesthesia is given the benefit of any doubts, nevertheless the book is obviously written by one who is actively practicing the clinical administration of anaesthesia and whose reasons for this leaning are sound and practical. There are chapters on the anatomy, physiology, experimental physics and pharmacology applicable to this subject. The various specific drugs with their pharmacology, advantages and disadvantages are discussed in detail. Differing techniques of administration are detailed and compared. Failures, complications, sequelae and results are discussed and methods proposed for their prevention or betterment. Another chapter deals with the advantages and disadvantages of this type of anaesthesia. The indications and contraindications are rationalized and the final conclusions arrived at are practical, sound and not overstated. The bibliography is copious and arranged according to author. Numerical references are not included.

The book is a very timely and complete one. It covers the subject fully and makes available in one volume information which otherwise would have to be sought from many different sources. Furthermore, it is practical and sound without undue over-emphasis. For the surgeon utilizing this form of anaesthesia, for the anaesthetist and for the experimentalist in this field, it should be most valuable.

R. T. S.

BOOKS RECEIVED FOR REVIEW

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